CORTISONE AND ACTH

IN CLINICAL PRACTICE

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IN CLINICAL PRACTICE

Under the General Editorship of

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With a Foreword by

THE LORD HORDER

GCVO MD FRCP

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FOREWORD

DR COPEMAN and his colleagues are to be congratulated on producing a practical and concise account of the present position of Cortisone and ACTH therapy Since Hench and his associates published their paper in 1949 on the effect of these two substances in the Rheumatic Diseases a considerable literature has accumulated and the doctor has great difficulty in finding from this literature the practical and everyday information he needs In such a rapidly changing field it is by no means easy for an author to choose the happiest moment to place his book on the bookshelf In this respect the appearance of *Cortisone and ACTH in Clinical Practice* is admirably timed containing as it does a consideration of hydrocortisone (compound F) and keeping in mind the probability that Cortisone will shortly be more freely available in Great Britain

Predominant interest is very naturally taken in the effect of Cortisone and ACTH in the Rheumatic Diseases and in dealing with this section himself Dr Copeman has most skilfully assessed the value of these substances and their association with other forms of treatment But although the Rheumatic Diseases take pride of place in any consideration of Cortisone and ACTH as therapeutic agents useful and indeed spectacular results can be obtained from their use in the treatment of several other conditions Dr Copeman has obtained the help of an impressive team of colleagues to cover the use of Cortisone and ACTH in these other specialized conditions

Professor Arnold Sorsby and Dr Mary Savory discuss eye conditions—a subject to be approached cautiously in our present state of knowledge but the practical nature of the work is retained and the doctor is clearly told what Cortisone may be expected to do and what it may not be expected to do

Dr F D Hart is responsible for the chapters on Endocrine Disorders and on Allergic Diseases The discussion of

Addison's disease is dealt with fully, since ACTH and Cortisone have clearly opened a completely new line of approach to this disease The case histories of patients with Simmonds's disease and Cushing's syndrome are most instructive

Dr Mitchell Heggs finds that it is now possible to generalize in regard to the skin conditions in which Cortisone and ACTH are indicated and strikes a note of warning against indiscriminate use of the hormones in this field

Dr J W Stewart writes the chapter on Blood Diseases ACTH and Cortisone produce marked effects on the haemopoietic system so that it is not surprising that a considerable amount of research has been done on the effect of these substances on blood diseases Results so far are still largely negative but the fact that remissions are reported in otherwise fatal conditions leaves room for the hope of more success in the future

Cortisone and ACTH in Clinical Practice is a work which *will surely prove of great value to the practitioner in providing* him with an authoritative answer to the many questions with which he will be faced

HORDER

March 1953

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PREFACE

EVER since the exciting discovery in 1949 by my friends Drs Phil Hench E C Kendall and Howard Polley of the Mayo Clinic of the therapeutic activity of Cortisone and ACTH the volume of world literature on this subject has swollen at an almost unmanageable rate Now seems to be the time to take stock of the consensus of current opinion

Although the sum of clinical experience with these hormones in the United States of America is far greater than is ours in Europe we have had to plan the use of our limited supplies and control our observations so carefully that we believe our opinions to be soundly based

This is the first book to endeavour to assess the place of these hormones in clinical practice In addition to having abstracted the relevant literature the writers of each chapter have had considerable personal experience in the use of Cortisone and ACTH

W S C COPEMAN

March 1953

' *Be not the first to cast the old aside*
Nor yet the first by whom the new is tried

Alexander Pope

CHAPTER 1

RHEUMATIC AND COLLAGEN DISEASES

History

Original conceptions of the adrenal glands

JUST under one hundred years ago Thomas Addison (1855) physician at Guy s Hospital drew attention to the clinical importance of the suprarenal gland He is still chiefly recalled for his clear description of the disease which is called after him and for the type of anaemia which bears his name but it may be that in the future he will be remembered for the fact that in 1855 he suggested that the adrenal gland is essential to life

This idea was supported by the French physician Brown Séquard (1856) from a number of animal experiments Young (1951) in a recent Addison Memorial lecture has pointed out how the idea of a secretion or hormone from the suprarenal or any gland for that matter was contrary to contemporary thought It was considered at that time that the nervous system alone controlled the functions of the body and hormones and their chemical composition had not yet been envisaged In addition the picture was clouded by the discovery of epine phrine in 1900 and as it was believed that each gland produced one substance only it was felt that the quota for the suprarenal had been accounted for

In the early years of this century there was an era of study of adrenal physiology but little interest was taken in this work from a clinical aspect

In 1924 Stewart wrote The cortex is the part of the adrenal essential to life How it exercises its function is utterly unknown Many of the conclusions drawn from physio logical experiments at that time were conflicting This was

due in the main to inexpert animal surgery which usually resulted in quick death after adrenalectomy so that only animals in a state of acute collapse were available for study This was pointed out by the same author who emphasized the need for a high standard of surgical technique and demonstrated that it was possible for adrenalectomized dogs to live for 10 days and that sound physiological studies could thus be undertaken

Evolution of the steroid hormones

In 1924-28 Smith (1930) demonstrated the intimate connexion between the pituitary gland and the adrenal cortex and by using his technique of hypophysectomy in the rat showed that removal of the pituitary caused a rapid atrophy of the adrenal cortex which could be repaired by transplants of anterior pituitary tissue

The active principle was later named adrenocorticotropic hormone (ACTH) In 1924 Evans demonstrated that pituitary extracts could also bring about adrenal repair in the hypophysectomized rat

In 1926 Rogoff and Stewart had prepared aqueous extracts of adrenal glands which produced rather uncertain results in experimental animals but soon afterward Swingle and Pfiffner (1930) showed that lipid extraction yielded a substance which would keep both adrenalectomized animals and patients with Addison s disease alive indefinitely

In the early 1930s an intense study was carried out into the chemical constituents of the adrenal cortex by three different groups of investigators led by Reichstein in Basle Kendall at the Mayo Foundation and Wintersteiner and Pfiffner at Columbia University and 28 crystalline steroids had been isolated by 1940 At that time there was little prospect that they would have much application in clinical medicine apart from substitution therapy in Addison s disease and this discouraged attempts at commercial production As so often in the history of medicine the outbreak of a war furnished a stimulus for it was rumoured that the German pilots were being given adrenal extracts to increase their fighting efficiency

Commercial production of cortisone and ACTH

The National Research Council of the United States of America called together a group of steroid chemists to consider the production of these substances on a commercial scale This work resulted in the preparation of cortisone (compound E) by Merck & Co Inc The method was originally worked out in Kendall s laboratory and later Sarett (1948) devised a method of increasing the yield a hundred fold At that time however in 1948 there still seemed little prospect of cortisone having much application to clinical medicine either for research or treatment Hench who had studied the problem of rheumatoid arthritis for many years and been particularly impressed with its suppression in pregnancy and after jaundice had however in 1941 discussed with Kendall the possibility of trying cortisone in this disease

Meanwhile further work was proceeding with ACTH and in 1943 Li Simpson and Evans working in California with sheep pituitaries and Sayers and his colleagues (1943) at Yale with pig pituitaries independently isolated proteins with high adrenocorticotropic properties The Armour Company sub sequently prepared pig protein ACTH on a commercial scale and other companies in the United States of America and in Great Britain and elsewhere have followed suit

First clinical application

On September 21 1948 at the Mayo Clinic the first injection of 100 milligrams of cortisone was administered to a woman with active old standing rheumatoid arthritis with dramatic results During that winter 15 more patients received the hormone and in the spring 5 patients with rheumatic fever In 1949 Hench Kendall Slocumb and Polley published their first account of the effects of cortisone and ACTH in these diseases The results were soon substantiated notably by Freyberg (1950) and Boland (1950a) in the United States and by Copeman and his colleagues (1950) in Great Britain Since then many long and short term studies have been published

In 1950 Hench Kendall and Reichstein were awarded the Nobel Prize in Medicine for their work in this field

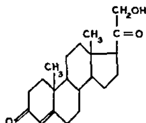
Since then three important developments have taken place *Cortisone has been found to produce the same effects when given by the mouth* Hydrocortisone (compound F) has been produced on a commercial basis and is undergoing clinical trials and a longer acting ACTH has been developed

Chemistry of cortisone and ACTH

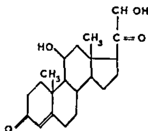
Kendall (1950) has told how almost 20 years were required for the chemical investigation of the cortical hormones In 1937 Steiger and Reichstein (1937) synthesized desoxycorticosterone from stigmasterol and as previously stated 28 steroids had been separated from the gland by 1940 These could be classified loosely into four groups First were certain sex hormones—androgens oestrone and progesterone which were not characteristic of the adrenal cortex second a group of physiologically inert steroids The third group which had marked physiological activity contained desoxycorticosterone compounds A B E (cortisone) and compound F (hydrocortisone) of Kendall and compound S of Reichstein These are all derivatives of Δ^4 pregnene and differ one from the other by the number and position of the hydroxyl and ketone groups attached to positions 11 and 17 of the steroid nucleus The fourth group a residue which remains after separation of the crystalline compounds is known as the amorphous fraction This substance is highly active is essential for the control of electrolyte metabolism but its chemical nature has not yet been established

Cortisone

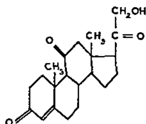
When the first clinical trials of cortisone were reported it seemed possible that other steroids which could be made more easily might have the same effect and a large number of such substances have been tried (Copeman and his colleagues 1950 Polley and Mason 1950) without success It appears that the formulae for cortisone and hydrocortisone are specific in their effect and that any deviation from them results in the loss of their therapeutic action in rheumatoid arthritis



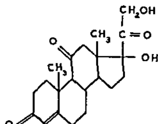
Desoxycorticosterone



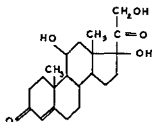
Corticosterone
(compound B)



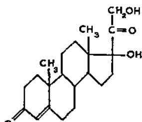
Dehydrocorticosterone
(compound A)



Cortisone
17 Hydroxy 11 dehydrocorti
costerone (compound E)



Hydrocortisone
17 Hydroxycorticosterone
(compound F)



17 Hydroxy 11 de oxycorti
costerone (compound S)

PHYSIOLOGICALLY ACTIVE ADRENAL STEROIDS

In 1950 Hench Kendall and Reichstein were awarded the Nobel Prize in Medicine for their work in this field

Since then three important developments have taken place Cortisone has been found to produce the same effects when given by the mouth Hydrocortisone (compound F) has been produced on a commercial basis and is undergoing clinical trials and a longer acting ACTH has been developed

Chemistry of cortisone and ACTH

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Cortisone

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of certain substances are known and that its most remarkable property is a high degree of stability towards heat and digestion by certain enzymes This indicates that the activity is associated with a small and stable molecular grouping and Li (1949) concludes that this fragment is a polypeptide with a molecular weight of about 1 200 Astwood and his colleagues (1950) have reported the preparation of a highly purified ACTH by extraction with glacial acetic acid with which a satisfactory response was obtained in rheumatoid arthritis with only 2 milligrams per day Long acting ACTH has been produced by a number of companies and is in the course of clinical evaluation The distribution of ACTH in the various body tissues has been studied (Sonenberg Keston and Money 1951) by administering the substance labelled with radioactive iodine to rats It was found that the hormone could be identified in the adrenals blood liver spleen and kidneys within a short time that the concentration fell rapidly and that the substance later became concentrated in the thyroid

Pituitary-adrenal relationship

Since Evans first demonstrated that certain extracts of the anterior pituitary caused adrenal hypertrophy in rats the pituitary–adrenal relationship has been extensively studied The knowledge we have of the control of adrenocortical secretion is largely derived from animal experiments and the difficulties of estimating this substance have been mentioned It has been shown that in the hypophysectomized animal the adrenal atrophies but that not all zones are affected equally the outer zone or glomerulosa is spared and electrolyte metabolism is less affected than other functions of the adrenal cortex In 1943 Brown reported the results of the administration of ACTH to two human subjects one showed an increase in urinary corticosteroids and the second glycosuria with a decreased glucose tolerance

Later reports (Forsham and his colleagues 1948 Prunty Forsham and Thorn 1948 Hills Forsham and Finch 1948 Forsham and his colleagues 1950b) show that a single injection of 25 milligrams of ACTH in humans resulted in a

By means of perfusion experiments on the isolated adrenal gland it has been shown (Zaffaroni Hechter and Pincus 1951) that corticosterone (compound B) and hydrocortisone probably constitute most of the active material secreted by the adrenal cortex

It has been estimated (Venning 1951 , Corcoran Dunstan and Page 1951) that from 30 to 60 milligrams of corticosteroids may be excreted daily by a normal man and Vogt (1947) calculates that under conditions of stress a dog may secrete cortical hormone at the rate of 54 milligrams per day which is equal to 350 milligrams per day for a man on a weight basis

Methods of measuring the amount of corticosteroids in the blood have been attempted by many workers but this has been proved extremely difficult to accomplish up to date Nelson and his colleagues (1951) have reported the estimation of hydrocortisone in the peripheral blood and give values varying between 4 and 10 micrograms per 100 millilitres of whole blood No evidence of the presence of cortisone in the blood was found by them

The commercial production of cortisone is a laborious process involving many steps Some of these have been simplified during the last few years and significant advances have come from Woodward Sondheimer and Taub 1951 at Harvard and Robinson (1951) at Oxford who have reported the total synthesis of the steroid nucleus

ACTH

The early work of Smith (1930) on this substance was con firmed in the 1930s and although there were many publications on methods of extraction it was not until 1942 that simulta neously from California Li Simpson and Evans (1943) and Yale (Sayers 1943) came reports of the preparation of a highly purified ACTH The chemical physical and biological data published by the two groups showed that both preparations were similar and it is now apparent that identical preparations of this substance can be obtained from sheep pig or ox pituitaries Henly (1949) reviewing the subject states that no complete amino analysis is yet available though percentages

this concept on studies of the lymphopenic response which is a rapid indication of anterior pituitary activity

It has been known for some time that changes occurred in the cholesterol and ascorbic acid content of the adrenal cortex under conditions involving increased cortical secretion The high concentration and labile nature of cholesterol had been recognized and Long (1947b) showed that the injection of a highly purified preparation of adrenocorticotropic factor into the rat caused a marked decrease in adrenal cholesterol and in fact as small amount as a 2 milligram injection of ACTH caused a 50 per cent reduction in cholesterol in 3 hours while other lipid constituents such as neutral fat and phospholipid remained unaltered This had reaccumulated in 24 hours and similar changes also occurred after a non fatal haemorrhage and other stress Neither response took place in the hypophy sectomized animal

The concentration of adrenal ascorbic acid is also regulated by the pituitary and a similar depletion occurs after one injection of ACTH and is replaced within 12 hours Long also emphasized the correlation which exists between the decline in adrenal cholesterol and ascorbic acid and other manifesta tions of adrenal cortical activity such as the increase in liver glycogen in fasting animals and the fall in lymphocytes Sayers and his colleagues (1944) have shown that the depletion of adrenal ascorbic acid following stress could be abolished by prior administration of adrenal cortical extract Of the crystalline steroids which they tested cortisone and hydro cortisone were the most potent followed by corticosterone (compound B) deoxycortone and progesterone Abelson and Baron (1952) showed that the depletion of renal ascorbic acid following unilateral adrenalectomy in rats can be inhibited by prior administration of cortisone intraperitoneally but that a high dose is required ACTH still caused depletion of adrenal ascorbic acid in the rats pre treated with cortisone Young has postulated that there are two separate factors in the hormone the adrenal weight increasing factor and the ascorbic acid depleting factor

marked fall in circulating eosinophils which was maximal in 4 hours a lesser fall in lymphocytes and an increased renal excretion of sodium potassium chloride and uric acid Repeated administration of ACTH (10 milligrams every 6 hours for 4 6 days) resulted in a rise in urinary corticosteroids and 17 ketosteroids These observations have formed the basis for Thorn s tests for adrenal cortical function

Physiological control

As there are no secretory nerves to the adrenal cortex the control over its function is probably exerted through the level of ACTH in the blood for although various conditions of stress will cause adrenal hypertrophy they cease to do so after removal of the pituitary The causes of an increased output of ACTH are also unknown but there are a number of conflicting theories on this subject It has been suggested by Long (1947a) that adrenaline is the responsible agent as this substance is secreted in many conditions of stress and because its infusion can be shown to increase cortical adrenal output He suggests (McDermott and his colleagues 1950) that the mechanism of the secretion of the adrenal cortex through the release of adrenocorticotropic hormone from the pituitary consists of two phases which may be independent The first or auto nomic phase depends on the reflex secretion of adrenaline which directly activates the anterior pituitary while the second or metabolic phase is based upon the rate of utilization of adrenal cortical hormones within the organism

The second suggestion by Sayers and Sayers (1947) is that in stress there is an accelerated utilization of cortical hormones by the tissues and that the low level of these hormones acts as a direct stimulus to the pituitary gland which releases an in creased supply of ACTH It has in fact been shown that depression of cortical activity results from the administration of large amounts of cortisone

Thirdly Harris and de Groot (1950) and Colfer de Groot and Harris (1950) have brought forward evidence that the production of ACTH is controlled by the higher centres via the hypothalamus and hypophyseal portal vessels They base

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This knowledge is used in the two common methods of bio essay of ACTH (1) The adrenal repair method in which the adrenals are allowed to regress for 10-14 days after hypophysectomy The gain in adrenal weight is then measured by the amount necessary to maintain the gland in its pre operative condition (2) The adrenal ascorbic acid depletion method (Sayers test) which is a more sensitive test

The general adaptation syndrome

There is no doubt that the relationship of the adrenal cortex and the pituitary is a mutually interdependent one but the full mechanism of its action is not yet fully understood The effects of stress on animals and particularly on the pituitary adrenal axis have been studied intensely in recent years and much of this work has come from Selye (1950 1952) with his pro pounding of the general adaptation syndrome and the aetiology of a wide variety of medical disorders of uncertain origin including the rheumatic group of diseases

Selye (1952) has told how he started with an interest in the condition of just being sick which occurs in a multitude of illnesses before specific signs of a particular disease are apparent Early work on rats made him suspect that there might be an ovarian principle causing the enlargement of the adrenal cortex involution of the thymico lymphatic apparatus and peptic ulceration It turned out that this could be pro duced by many agents varying from pituitary extract to formalin His general adaptation syndrome (G A S) consists of three stages the alarm reaction the stage of resistance and the stage of exhaustion He compares the syndrome with that of inflammation both are non specific reactions which go through a series of distinct stages and both can be elicited by a variety of agents Selye found that the more an animal was injured by heat cold infections and starvation the more the adrenal cortex grew Some manifestations of the G A S such as eosinopenia and lymphopenia were prevented by adrenalectomy while others such as gastro intestinal ulceration and general wasting became more pronounced

Diseases of adaptation

This work resulted in the highly controversial theory of the diseases of adaptation which include nephrosclerosis hypertension and the rheumatic and other collagen diseases Selye considers that stress invariably stimulates the pituitary adrenal system but that this process may have different results one depending on ACTH and the gluco corticoids inhibits inflammatory response whereas the other depending on different pituitary principles and the mineralo corticoids produces it The type of response is said to depend on conditioning circumstances such as heredity dietary factors and previous exposure to various pathogens Selye believes that the diseases of adaptation are due not to hormones alone nor to any one pathogen alone but to the development of pathogenic situations in which many factors participate

This is virtually a new theory of medicine and little of it is factual up to date The conception has been much criticized particularly by Rosenberg Woodbury and Sayers (1952) who challenge the whole conception of the general adaptation syndrome They repeated many of Selye s experiments and conclude that the G A S conception has little basis in experimental fact They consider that the action of the cortical steroids in mesenchymal disease is probably one aspect of a general inhibitory effect of cortisone and related steroids upon all inflammatory processes regardless of the inciting agent be it infections traumatic chemical or antigenic They state that there is no justification in concluding that the pathologic change in mesenchymal tissue diseases in man and in deoxy corticosterone treated rats have a common aetiology simply because ACTH and cortisone exert a favourable influence in both

Physiology of the adrenal cortex

Concern has been expressed that prolonged treatment with cortisone or ACTH as may be necessary in rheumatoid arthritis for instance might have a permanently damaging effect on the suprarenal cortex There is as yet insufficient evidence to be dogmatic on this point and in fact little is known of the

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it has been suggested that the drug would affect the fixation of sulphate by the tissues and experimental work (Layton 1951a) has seemed to confirm this Suppression of the cellular enzyme systems has been postulated as a possible mode of action and evidence (Anderson and his colleagues 1951) suggests that ACTH and cortisone inhibit the hyaluronidase enzyme system by the agency of sulphydril deprivation

Physiology of cortisone and ACTH

The majority of the physiological properties of cortisone and ACTH are similar Sprague (1951) in an excellent review has pointed out that their effects are broader in scope than any other hormones previously employed in clinical medicine and that as yet only a superficial description is possible

Maintenance of life and ability to work and to resist stress

Relatively large doses of cortisone are required to main tain life in adrenalectomized animals and when compound E was first isolated it was thought to be physiologically inactive as it failed to maintain life in adrenalectomized dogs owing to insufficient dosage The value of cortisone in the treatment of Addison s disease is now established and for this relatively small amounts are needed It has also been shown to be effective in the ability to sustain work in adrenalectomized rats being more powerful than all other adrenal steroids save hydrocortisone (compound F) Ingle Nezamis and Morley (1951) have shown by work performance tests on rats that hydrocortisone is about twice as effective in this respect as cortisone Cortisone will protect these animals against many forms of stress such as injection of typhoid vaccine cold and various anaphylaxis like and hypersensitivity reactions

Carbohydrate metabolism

ACTH cortisone and hydrocortisone exert their main physiological effect on carbohydrate metabolism In 1941 it was shown (Ingle 1941) that cortisone will induce hyper glycaemia and glycosuria in force fed rats and this has been confirmed many times since Later it was observed (Kobernick and More 1950) that a diabetic state and hydropic changes

behaviour of the cortex throughout normal life Work done on newborn infants Klein and Hanson (1950) shows that in the first week of life there is only a small fall of circulating eosinophils after ACTH but that after 7 days the response approximates to the normal In the elderly (Solomon and Shock 1950) there is a significantly smaller response to ACTH than in young adults as shown by the eosinophil response and similar tests but it seems the ability of the adrenal cortex to secrete steroids is not grossly impaired in old age

It is known that during administration of cortisone there is a diminished output of corticoids by the suprarenal and adrenal cortical failure has been reported (Proctor and Rawson 1951) after combined cortisone and ACTH administration in which the destruction of the cortex seemed to be caused by giving ACTH immediately after cortisone

In animals studied (Stebbins 1950) during and after cortisone injections for 10–42 days the inner cells of the cortex showed marked depletion of lipoid and ketosteroid like material but the glandular parenchyma had resumed a normal appearance within 17 days of stopping the drug

O Donnell Fajans and Weinbaum (1951) studied the human adrenal in patients who had been given ACTH prior to death The zona glomerulosa appeared narrow and ill defined but some of the cells were hypertrophied The zona fasiculata and zona reticularis showed evidence of hypertrophy The adrenals of 5 patients who received cortisone in moderate amounts were examined and it was found that while the two inner zones were atrophied the outer glomerulosa zone was broadened In a patient who had had no cortisone for 17 days there was evidence of regeneration and the authors state their findings indicate that the influence of cortisone on the adrenal is reversible and that the gland can respond to stress after this drug has been given In spite of an immense amount of research both in American laboratories and elsewhere the mode of action of cortisone and hydrocortisone is still obscure There is reason to think that the drug acts at the tissue level but how it brings about its effects is unknown Since cortisone has been found to have an inhibitory action on wound healing

whose daily insulin requirements rose from 10 to 15 units Three days after the cortisone was withdrawn only 10 units were required again Other workers (Browne and his colleagues 1950 Perera and his colleagues 1949) have noted increased insulin requirement with cortisone in diabetics

It has been suggested that the diabetogenic effects of these hormones may be due to a deficiency of the insulin producing mechanism and work on cases of Cushing s syndrome lends support to this theory (Forsham and his colleagues 1950a) Another important fact was noted by Sprague and his associates (1950) who found that in 2 of 4 patients showing impairment of carbohydrate tolerance under the influence of cortisone there was a family history of diabetes

It has been suggested that the glycosuria induced by these hormones may be due at any rate in part, to a lowering of renal threshold for sugar and a number of observations (Conn Louis and Wheeler 1949 Sprague and his colleagues Kass Ingbar and Finland 1950) have been reported in which pronounced glycosuria has been found with only mild hyperglycaemia Sprague (1951) has concluded that as the effects only persist as long as the hormones are being given or for a short time afterwards it is only necessary to carry out treatment for the glycosuria should it occur but that particular caution is necessary for diabetic patients

Electrolyte and water metabolism

The effect of cortisone and ACTH on electrolyte balance is variable depending on dosage and species Thorn Engle and Lewis (1941) showed that single doses of cortisone in the dog and rat caused increased excretion of sodium and chloride Later (Levitt and Bader 1951) it was found that in the rat this only lasted for 3 days and that then the normal balance was restored Cortisone evidently has comparatively weak electrolyte activity That the changes are variable is undoubted and both cortisone and ACTH can cause sufficient retention of sodium chloride and water on occasions to cause oedema Frequently we have seen this in the early stages of hormone administration and subsidence of the oedema later without

in the islet cells of the pancreas could develop in rabbits during the administration of 20 milligrams of cortisone daily Cortisone has been found to lessen the sensitivity to insulin in patients with Addison s disease and to intensify hyperglycaemia glycosuria and ketonuria in patients who have both diabetes and Addison s disease

By animal work it has been shown that gluconeogenesis is increased by these three substances with an increased storage of glycogen in the liver It has been found that part of the glycogen results from an increased breakdown of protein and also of amino acids Ingle (1950) has reported that in animals the effect of treatment with adrenal steroids may not be sustained throughout prolonged administration Glycosuria is not usually produced except after a latent period of 72 hours or more and the normal animal is capable of adaptation to the continued administration of a diabetogenic dose of either ACTH or cortisone so that the glycosuria may disappear The amounts of the hormone used to induce frank diabetes in rats are many times greater for their relative weight than those used therapeutically in man In patients given therapeutic doses alterations in carbohydrate metabolism if they occur at all have not been pronounced

There have however been a few instances in which diabetogenic effects of cortisone or ACTH have been reported Pearson and Eliel (1950) have observed a diabetic state and ketosis in a young man given large doses of cortisone for acute leukaemia Conn Louis and Wheeler (1948) induced a temporary diabetic state in 3 normal adults by the administration of 120–150 milligrams of ACTH daily for 8–10 days and Glyn (1951) has reported the induction of apparently permanent diabetes by ACTH However such observations are exceptional for the vast majority of patients treated with cortisone or ACTH have shown no significant impairment of carbohydrate tolerance

On the other hand it would be anticipated that cortisone or ACTH might intensify pre-existing diabetes and this has proved to be the case Boland and Headley (1949) reported the case of a patient with rheumatoid arthritis and diabetes

that there was an accompanying increase in urinary nitrogen but that there was an adaptation on continued administration Other workers have noted both in health (Conn Louis and Wheeler 1948) and in various diseases (Thorn Prunty and Forsham 1947 Bartter and his colleagues 1950 Pearson and his colleagues 1949 Sprague and his colleagues (1950) the increased urinary output of nitrogen during administration of the hormones In some cases it was found that a doubling of the protein intake resulted in a change from a negative to a positive nitrogen balance There is presumably a relationship between this and the anti anabolic effect which has been postulated by Albright (1943) and which may be pertinent to the osteoporosis which is caused by these substances and to the atrophy of collagen fibres which has been noticed under experimental conditions There is evidence that growth may be inhibited by these hormones Follis (1951) has shown that although small doses did not affect growing bones in rats large doses resulted in a flattening of the growth curve and the bones showed an area of increased density which was attributed to a disturbance of normal osteolytic activity Other workers (Silverman Day and Blodi 1951) report retardation of growth when premature infants were given ACTH for retrolental fibroplasia The fact that cortisone produces growth inhibition in the chick embryo newly hatched chick and new born mouse has been used (Karnofsky Ridgway and Stock 1951) as a basis for investigating steroids for cortisone like action

Plasma proteins have been studied particularly because of their disturbance in a number of collagen diseases and there is no doubt that cortisone and ACTH are capable of correcting the abnormal proportions of these and particularly of the globulin fraction Hench Kendall Slocumb and Polley (1949) reported this fact which has been abundantly confirmed In liver disease (Karnofsky Ridgway and Stock 1951) ACTH administration has resulted in a fall of concentration of *gamma* globulin a rise in albumen and a fall in total protein Both cortisone and ACTH have been found to cause an increase in urinary uric acid and this has been used particularly in the

change of dose The matter has been clarified by the work of Sprague and his colleagues (1950) who observed in balance studies that there was a *prompt retention of sodium and* chloride during the first few days of administration of ACTH *followed by increased excretion so that the balances became* negative while the hormone was still being given

Levitt and Bader (1951) have carried out studies on water metabolism during administration of these hormones by determining the inulin space distribution Despite rigid salt restriction they found that both cortisone and ACTH induced in each patient a progressive increase in approximately isotonic extracellular volume of 20-40 per cent In 3 patients studied at frequent intervals during the course of hormone treatment this increase in extracellular volume reached its maximum in 8-9 days after the onset of treatment and then gradually decreased to control values despite the continuation of therapy Neither the progressive increase nor subsequent decrease of *extracellular fluid and total extracellular electrolyte* was reflected in body weight changes or over all sodium and *chloride balances The observed increase in plasma volume* was much less and averaged 9 per cent This work suggests *that cortisone and ACTH produce a transient but significant* shift of water sodium and chloride into the measurable extracellular space

Increased excretion of potassium has been shown to occur with cortisone and ACTH with resulting muscle weakness and myocardial changes manifested by the electrocardiogram With these hormones a hypochloraemic hypopotassaemic alkalosis has been seen to occur in Cushing s syndrome Sprague and his colleagues (1950) have shown that this can occur in man with 100 milligrams of ACTH for 12 days Cortisone produced little change of this kind at 100 milligrams a day but when raised to 200 milligrams a day a similar event might occur under experimental conditions

Protein metabolism and growth

In their early work on the production of diabetes in rats by cortisone and ACTH Ingle and his colleagues (1950) found

have found that on prolonged ACTH the level rose above normal Animal work has shown that in the rabbit 16 days of cortisone will produce a marked lipaemia with the presence of fat droplets in the serum (Piliero Landau and Gordon 1950) Aldersberg Schaefer and Drachman (1950) have reported that in patients given continuous cortisone for an average of 25 days there was an elevation of serum cholesterol of some 20 per cent , with ACTH for an average period of 48 days there was an elevation of serum cholesterol of 33 per cent Such hypercholesterolaemia developed three times as frequently in the patients who had prolonged courses of therapy as in those who received shorter courses These authors noting the assumed relationship between hypercholesterolaemia and atherosclerosis discuss the possible development of the latter in patients treated with these hormones Prolonged observation of many patients on a long term programme with these drugs will be necessary before any conclusions can be drawn

Effects on specific tissues

The blood

In the early investigation of the effects of cortisone and ACTH in rheumatoid arthritis it was noted that as well as improvement in the joint condition there was a similar change in the accompanying anaemia Studies have since been undertaken to investigate the effect of these hormones on the haemopoietic system Work in adrenalectomized rats has shown that an anaemia is apparent in the peripheral blood up to 25 per cent 2–3 weeks after operation and that this can be prevented by administration of adrenal cortical extract (Piliero Landau and Gordon 1950) Finch and his colleagues (1951) noted that in cases of rheumatoid arthritis which were treated with these hormones for 21 days there was a significant reticulocytosis with an increase in haematocrit and total circulating red cells Bone marrow studies before treatment showed moderate depression of the erythroid series and this was restored to normal These authors suggest that the improvement in the anaemia is a reflection of the control of the underlying disease

investigation of cases of gout in which there is reported to be a miscible pool of uric acid as much as thirty times above normal (Benedict and his colleagues 1950)

Holbrook and his associates (1950) have reported a rise in the urinary excretion of several amino acids during each remission of rheumatoid arthritis whether occurring spontaneously or induced by cortisone ACTH pregnancy or jaundice Other workers (Stephens and his colleagues 1950) have noted an increase of free histidine in patients with rheumatoid arthritis during cortisone and ACTH administration In animal work (Ingle Prestrud and Nezamis, 1950) with cortisone a rise in plasma amino acids has been reported and from patients having ACTH (Roberts Ronzoni and Frankel 1951)

The dosages of cortisone and ACTH now being employed for therapeutic purposes probably do not cause any pronounced upset of protein metabolism

Fat metabolism

One of the most characteristic features that we have observed in patients being investigated with continuous administration of either cortisone or ACTH for long periods is rounding of the face and less often deposits of fat in the supraclavicular regions over the upper dorsal vertebrae and elsewhere A relative increase in depot fat under similar circumstances has been reported by Winter Silber and Stoerk (1950) Such changes are characteristic of patients with Cushing s syndrome though in none of our cases have they been as marked

Stoerk and Porter (1950) noted that in adrenalectomized rats on a starvation diet 2 milligrams of cortisone daily reduced the loss of weight to one fourth The blood lipids have been extensively studied in connexion with these hormones Conn and his colleagues (1950) found a decrease in serum cholesterol in normal subjects after several days administration of ACTH and postulated that the serum cholesterol constitutes a source of material for the synthesis of cortical hormones when the reserve supply in the adrenal has become depleted However other workers (Aldersberg Schaefer and Drachman 1950)

to have normal adrenals there is a 50 per cent or greater diminution A test has been suggested (Roche Thorn and Hills 1950) as a means of estimating prognosis in surgical patients with doubtful adrenal cortical function This test of a 50 per cent fall in the level of circulating eosinophils has also been used to check the adequacy of therapeutic doses of ACTH Studies on bone marrow (Rosenthal and his colleagues 1950) have shown that although there is a fall in circulating eosinophils there is a significant increase in these cells in the bone marrow suggesting that the hormones increase the rate of their removal from the blood without affecting the production With cortisone and hydrocortisone the eosinopenia is less marked It has been observed (Stoerk and Solotorovsky, 1950) that there is no diminution in mitotic activity in the atrophic thymus of rats during administration of cortisone which suggests that the loss of tissue is due to accelerated destruction of lymphocytes and Conn (1950) found that in patients with rheumatoid arthritis given 200 milligrams of cortisone daily the fall in the number of these cells was delayed In prolonged studies with cortisone in rheumatoid arthritis there has been seen a diminution of 60–70 per cent in circulating eosinophils in all cases but in some the lowest level was not reached until the fifth day (Copeman and his colleagues 1952) In the same investigation the escape of eosinophils to levels above the original was reported which occurred in 2–4 weeks and this has been seen by other observers There is also disagreement on the effects of these drugs on the coagulability of the blood

Some investigators (Cosgriff Diefenbach and Vogt 1950) have reported shortening of the clotting time others (Smith and his colleagues 1950) lengthening and a third (Fahey 1951) no change

Although lymphopenia in humans is not always observed following the administration of these hormones there is no doubt that in animals given high doses this finding is constant and is accompanied by atrophy of the thymus spleen and lymph nodes

rather than a primary stimulation of the bone marrow More prolonged investigations in rheumatoid arthritis have shown that with cortisone there was an increase in reticulocytes during the second week and this was followed by a rising haemoglobin and red cell count until normal levels were reached (Copeman and his colleagues 1952) At the same time the cells showed a full complement of haemoglobin and microcytosis if it had been present disappeared The total leucocyte count rose and a leucocytosis was observed at some stage during administration which contrasted with the normal or subnormal level before treatment The neutrophil granulocytes showed the most spectacular rise and a lymphopenia which has been observed by other workers was not observed at any stage The changes in the blood platelets were not so dramatic but appeared to follow the granulocytes rising and falling with the level of these cells The plasma volume was also studied in these investigations and this showed a decrease although all the patients in the investigation had some degree of fluid retention as shown by fluid balance estimations and increase in weight (*see* Fig 1)

Initially during the period of rapid change the haemoglobin and packed cell volume showed similar variations to the plasma volume but as the latter returned to its normal level rather slowly the red cells increased There has been some disagreement on the production of lymphopenia in patients by these hormones and some workers (Heilman 1945 Feldman 1950) have observed destruction of these cells but others (Thorn and Forsham 1949 Sprague and his colleagues 1950) have failed to demonstrate this change either in Addison s disease or in rheumatoid arthritis

A fall in the level of circulating eosinophils more marked with ACTH than with cortisone or hydrocortisone has been universally recognized and is used as a basis for testing for normal adrenal response Thorn and his associates (1948) described a test for adrenal cortical insufficiency based on the eosinopenic response to a single injection of 25 milligrams of ACTH In patients with Addison s disease there is no decrease of circulating eosinophils in 4 hours whereas in subjects known

Antibodies

The effect on the lymphocytes may be important from another aspect as Dougherty White and Chase (1944) have presented evidence that an increase in the secretion of the adrenal cortex releases stored immune bodies by causing fragmentation of lymphocytes and thereby a rise in circulating antibody globulins Antibody production has been studied by Mirick (1951) who reports that following vaccination with pneumococcal polysaccharides antibody production was not depressed Massell and his colleagues (1950b) reported that ACTH did not affect the usual antistreptolysin and *gamma* globulin response to streptococcal infection It has been found with cortisone that there was no change in the naturally occurring *alpha* and *beta* antibodies antistaphylo coccal toxin titres or Rose s differential agglutination titres in cases of rheumatoid arthritis (Copeman and his colleagues 1952) The Arthus reaction in rabbits is inhibited by corti sone and ACTH (Germuth and Ottinger 1950) Soffer and his colleagues (1950) observed that administration of ACTH to rabbits before the provocative injection of meningo coccus toxin completely inhibited the Schwartzman pheno menon which is characterized by a severe confluent haemor rhagic necrosis at the site of an initial intradermal injection following the intravenous administration of a provocative dose

Blood sedimentation rate

As this estimation is one of the recognized methods of measuring the activity of rheumatoid arthritis the effects of cortisone and ACTH on the erythrocyte sedimentation rate have been specially studied The Mayo Group (Hench and his colleagues 1949) reported early that the clinical response to the hormones in rheumatoid arthritis was accompanied by a return to normal of the sedimentation rate in about 2 weeks Further study has shown that as the dose is dropped to a maintenance level the sedimentation rate rises again but while the disease remains suppressed the rate though above normal is below the original level Copeman and his colleagues

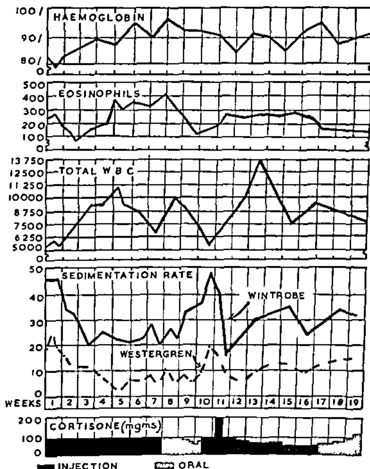


FIG 1 —Haematological responses with cortisone
(By courtesy of the British Medical Journal)

occurs after various types of tissue damage and stress such as cold x ray irradiation mitotic poisons protein shock and insulin hypoglycaemia all of which cause adrenocortical stimulation The effects of ACTH on capillary resistance were therefore studied in cases of rheumatoid arthritis ankylosing spondylitis and lupus erythematosus with ACTH and cortisone The predicted correlation between it and the eosinopenia was found and patients with hypopituitarism (Robson and Duthie 1952) who were noted to have abnormally low capillary resistance which was not raised by single injections of ACTH but responded to repeated doses Desoxycorticosterone caused lowering of the resistance and a number of other steroids which have been shown to have no clinical effect in rheumatoid arthritis (Copeman and his colleagues 1950, Polley and Mason 1950) such as pregnenolone and progesterone did not alter the capillary resistance

A number of investigators have found evidence that adrenal cortical extracts adrenal cortical insufficiency and certain steroids can influence the permeability of membranes

Some workers (Benditt and his colleagues 1950) have shown that the increased capillary permeability produced by intravenous administration of hyaluronidase in rats was largely inhibited by 5 days pre treatment with either ACTH or cortisone From this work they suggest that cortisone does not act directly on the connective tissue or that it is modified by some cellular process to another compound which acts directly on the tissue or enzyme The spreading action of hyaluronidase has been studied and in mice it was found that the dermal spread of india ink was enhanced by adrenalectomy and that adrenal cortical extracts would inhibit this Seifter Baeder and Dervinis (1949) observed that hyaluronidase slows osmosis and abolishes the semipermeable nature of membranes prepared from the excised bladder of rabbits The effects of hyaluronidase and steroids upon permeability were also studied with regard to the speed of absorption of phenolphthalein injected into the ankle joints of rabbits and the time taken for its excretion into the bladder Hyaluronidase

(1952) studied this aspect on prolonged investigation and concluded that this estimation was of little value in assessing the activity of rheumatoid arthritis during cortisone administration

Bagnall (1951) had described the paradoxical behaviour of the erythrocyte sedimentation rate with cortisone how in some patients the rate falls before there is clinical improvement while in others this occurs much later and he has seen the rate rise under the hormone in spite of clinical response Fletcher, Dauphineer and Ogryzlo (1952) have studied the relationship between the erythrocyte sedimentation rate and the plasma fibrinogen in patients with rheumatoid arthritis and the effect of cortisone and ACTH on these They find that the erythrocyte sedimentation rate is a rough index of the blood fibrinogen level in patients with this disease where there is no abnormality in the globulin content and in the absence of severe anaemia The raised fibrinogen level appears to be a reaction to the inflammatory process or tissue injury In the cases they studied the sedimentation rate seemed to be an index of the intensity of the disease reaction rather than of the severity or gravity of the disease itself and comparable to fever or leucocytosis With the fall in plasma fibrinogen and the erythrocyte sedimentation rate which accompanies a partial or complete remission induced by ACTH or cortisone in rheumatoid arthritis the relationship of the erythrocyte sedimentation rate and fibrinogen is maintained except that there is a lag in the sedimentation rate fall of from 24 to 48 hours and this occurs also in the relapse on withdrawal of the hormones Fearnley and Bunim (1951) have studied the sedimentation rate and plasma fibrinogen in healthy young adults given 1 injection of ACTH and postulate a non specific effect of the hormone in a lowering of the sedimentation rate This suggests that a normal sedimentation rate may not be a reliable index of absence of rheumatic activity

Capillary resistance and permeability of membranes

Robson and Duthie (1950) observed that an increase in capillary resistance as measured by a negative pressure method

dogs and found no disturbance of wound healing with cortisone They also found no delay in healing in patients receiving cortisone who underwent major surgical procedures and this is the experience of most clinicians including ourselves It evidently requires large doses of the hormones to bring about this change and only certain animals are affected in this way

Mesenchymal tissue

Hench and his colleagues (1949 1950) in two reports have mentioned changes in the synovial membrane in rheumatoid arthritis After systemic cortisone administration the first synovial membrane from a knee showed evidence of healing but was not normal later similar cases were reported and in each instance there was histological improvement with a decrease in the number of plasma cells and lymphocytes reduction of papillary tufting and lessened oedema and necrosis

Clark, Ropes and Bauer (1950) found a lowered cell count of the synovial fluid and a rise in viscosity as a result of the administration of ACTH in rheumatoid arthritis Hollander Stoner and Brown (1950) measured the intra articular temperature in joints under treatment with the hormones and found a significant fall On continued administration the intra articular temperature fell to within normal limits We have observed the nodules of rheumatoid arthritis under prolonged administration of these drugs and though there is usually a marked softening the histological appearance though showing lessening of oedema and inflammatory changes has in no case reverted to normal

Animal work (Michael and Whorton 1951) has shown that under the influence of these hormones all the tissue components of the inflammatory reaction are delayed vascular margination of leucocytes migration of leucocytes from blood vessels and the formation of fibrin and oedema are altered Layton (1951b) has suggested that the palliative action of cortisone in the connective tissue diseases may be due to its inhibitory effect on the synthesis of chondroitin sulphate which is a constituent of the connective tissue ground substance

and DOCA were shown to increase the permeability whilst cortisone and some other steroids decreased it

Wound healing

The effect of cortisone and ACTH on wound healing and on mesenchymal tissue is of particular interest to those interested in the rheumatic group of diseases as from this we may be able to learn the mode of action of these hormones at the tissue level in the collagen diseases Baker (1951) studied the action on the skin and found that it was possible to demonstrate a local action of adrenocortical hormones using doses so small that the amount absorbed into the blood stream was insufficient to cause a systemic effect He found that prolonged direct application of adrenal extract to the skin caused thinning of the dermis with involution of fibroblasts a temporary retardation in the formation of granulation tissue which could not be maintained indefinitely These changes were also found in the tissues surrounding implanted pellets of pure adrenal steroids Howes and his colleagues (1950) studied the course of wound healing in the ears of rabbits given large doses of cortisone They found that after 8 days the blood vessels were completely uncovered by granulation that subsequently a small layer of fibrin formed on the wound and the epithelization was less than in the control group There was no increase of surface infection When cortisone was discontinued the granulations increased Healing of fractures in rabbits was also delayed In further work Ragan and his colleagues (1950) suggest that the catabolic effects of the hormones on mesenchymal tissue might be responsible for these defects of the healing process Bangham (1951) studied the effects of cortisone in wound healing in different animals and found that while in the rat and rabbit this was delayed there was no similar change in guinea pigs He found that cortisone will inhibit the skin reactions to histamine and leucotactic peptides and suggested this may be the mechanism whereby inflammatory processes are subdued in rheumatic fever and rheumatoid arthritis Other workers (Cole and his colleagues 1951) have studied the problem in

renal damage beforehand This undoubtedly should be done at any rate until much more is known of the effects of the hormones on arterial pressure and the cardiovascular system

Measurement of the end products of adrenal secretion

The methods of measurement of such products as the 17 ketosteroids and corticoids in the urine are undoubtedly not satisfactory at the present time in spite of the large volume of work carried out on this aspect of adrenal physiology

Cortisone in a dosage of 100 milligrams a day produces an initial fall in the volume of 17 ketosteroids in the urine and this is followed by an increase and a levelling off with a gradual diminution to low levels on prolonged dosage which persists for several weeks after the administration is stopped This suggests depression of the adrenal cortex With 200 milligrams of cortisone a day higher levels of ketosteroids are obtained Much of this is probably derived from exogenous cortisone With ACTH there is a prompt and pronounced increase in 17 ketosteroids

Both cortisone and ACTH cause an increase in the levels of urinary corticoids as at present measured Sprague and his colleagues (1950) recovered a large amount of hydro cortisone from the urine of patients who had been given ACTH Kellie (Copeman and his colleagues 1952) studied the steroid metabolism during prolonged cortisone administration in rheumatoid arthritis The pre treatment values of urinary formaldehydogenic steroids (corticoids) in four cases were below the normal range for the method and on administration of cortisone a small increase into the normal range was observed A further increase exceeding the normal range was noted when the daily amount was raised to 200 milligrams

Pre treatment levels of 17 ketosteroids were at the lower limit of the normal range and there was a variable response to administration of the hormone after an initial fall in the output A differential analysis of the 17 ketosteroids was carried out in some cases and it was found that the ratio of etiocholanolone and androsterone was significantly raised in some compared

Blood pressure

In view of the fact that low blood pressure is a feature of Addison s disease it might be expected that ACTH and cortisone would cause hypertension This is of great importance for instance in diseases such as rheumatoid arthritis where suppression of the disease can only be obtained by continuous administration of the hormones for very long periods if not indefinitely Much work has been done on this aspect because animal studies showed that cortisone could cause lesions in the kidneys and in fact had hypertensive effects in rats (Knowlton and his colleagues 1949) under some circumstances Perera and his colleagues (1950) undertook clinical and metabolic studies in a woman with hypertension who was given a high dose of cortisone (200 milligrams per day) for a month Following a preliminary rise there was a small but definite decline in blood pressure while the patient was receiving the drug and this persisted for several weeks after it had been discontinued The same author (Perera 1951) later reported on 33 patients with normal blood pressure under the same conditions Only one showed any change However in 10 patients with renal involvement there was a rise in both systolic and diastolic pressure within a few weeks of commencement of cortisone administration regardless of the presence or absence of hypertension before treatment In rats and dogs however (Grollman and Konnerth 1951) in whom hypertension was produced by the ligation of one kidney no change was found with cortisone administration

Although cortisone and ACTH have been reported as causing hypertension in a number of patients with a variety of disease these have been exceptional save in cases of disseminated lupus erythematosus Soffer Levitt and Baehr (1950) observed hypertension in all of 10 such patients and congestive heart failure occurred in 4 during treatment with cortisone We have not observed a significant change in blood pressure in any patient with rheumatoid arthritis during prolonged administration of either cortisone or ACTH but we have been careful to exclude evidence of hypertension or

of a substance such as cortisone in a stubborn chronic disease like rheumatoid arthritis than in rheumatic fever symptoms of which may disappear spontaneously As they wrote at that time (1949) it may also be asked even if the rapid dis appearance of fever tachycardia polyarthritis abnormal sedimentation rates and electrocardiographic changes were caused by the compound in what way if any is compound E (cortisone) superior to the infinitely less expensive salicylates and of what real value is it if the cardiac complications are not prevented controlled or healed? They also pointed out that many false deductions had been made as to the efficacy of certain measures in rheumatic fever because so few careful observations had been made on the natural course of the untreated disease They expressed the hope that cortisone would have a beneficial effect on the cardiac muscle and valves in view of its effect on the polyarthritis and tachy cardia and stated that their results were encouraging

The question as to whether cortisone and ACTH are superior to salicylates in rheumatic fever has not yet been answered At first supplies of the hormones were so small that few studies could be undertaken but more recently publications have been appearing in greater numbers Massell and his colleagues (1950b) reported on 10 patients with severe rheumatic fever and carditis treated with ACTH The minimal daily dose to suppress symptoms was found to be between 20 and 50 milli grams a day All but 1 of the 10 patients improved remarkably and the rheumatic process became quiescent in 5 of the patients in periods of 4–10 weeks There was a tendency for the hormone to cause retention of fluids and other adverse effects reported were mental depression abdominal cramps acne rounding of the face and headache

From Canada a case of rheumatic pancarditis was reported (Bell Bell and Wilson 1950) in which a high initial dose of cortisone was administered after salicylates had failed to affect the fever Within 48 hours after the hormone had been started the temperature became normal and the gallop rhythm and friction rub had disappeared After 16 days the drug was discontinued with relapse of fever and arthritis and return of

with normal subjects although this is not necessarily of significance in rheumatoid arthritis In no case was this ratio restored to normal during the administration of cortisone

Dobriner and his colleagues (1950) have also studied the differential ketosteroid pattern in various diseases and they report in the only case of arthritis studied the finding of an abnormal adrenal metabolite—17 hydroxy pregnenolone This substance is found quite regularly in cases of adrenal hyperplasia and adrenal tumour so they surmise that this one patient with arthritis had an adrenal dysfunction

Chemical estimations of the corticoids in adrenal venous blood have shown that hydrocortisone and corticosterone (compound B) are by far the major secretory products of the adrenal cortex in many mammalian species Simpson Tait and Bush (1952) have published evidence of the presence of a salt retaining hormone in the adrenal veins of monkeys and dogs

RHEUMATIC FEVER

Soon after their original paper on the effects of cortisone in rheumatoid arthritis Hench and his colleagues (1949) at the Mayo Clinic published a preliminary report on the effect of the hormone in the acute phase of rheumatic fever in 3 patients They found that with cortisone administration the fever disappeared in a few days the joints became symptom free at the same time and the blood sedimentation rate reverted to normal in about 2 weeks Tachycardia was also abolished and in fact a bradycardia was observed In one case an enlarged heart reverted to normal size after 13 days In one of these cases a cardiac murmur developed during administration and other abnormal heart sounds were unchanged In the electrocardiographic observations in 2 of the patients a prolonged P R interval was restored to normal and in 1 other case RS-T and T wave changes disappeared In the laboratory investigations the haemoglobin rose the leucocytosis varied but remained at a level above the normal range and the plasma proteins were slightly increased Hench and his colleagues pointed out that it is easier to assess the value

of a substance such as cortisone in a stubborn chronic disease like rheumatoid arthritis than in rheumatic fever symptoms of which may disappear spontaneously As they wrote at that time (1949) it may also be asked even if the rapid dis appearance of fever tachycardia polyarthritis abnormal sedimentation rates and electrocardiographic changes were caused by the compound in what way if any is compound E (cortisone) superior to the infinitely less expensive salicylates and of what real value is it if the cardiac complications are not prevented controlled or healed? They also pointed out that many false deductions had been made as to the efficacy of certain measures in rheumatic fever because so few careful observations had been made on the natural course of the untreated disease They expressed the hope that cortisone would have a beneficial effect on the cardiac muscle and valves in view of its effect on the polyarthritis and tachy cardia and stated that their results were encouraging

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gallop rhythm which was suppressed by a further month s treatment at a lower dosage Barnes (1950) studied acute rheumatic fever during the first attack in 10 cases 7 were treated with cortisone and 3 with ACTH Cardiac enlargement was not seen after discharge from hospital for a period of 10 months but 5 patients had developed apical systolic murmurs In patients studied during recurring attacks of acute rheumatic fever there was reduction in cardiac size during cortisone administration He concluded that cortisone and ACTH can suppress the acute manifestations of the disease in 3 weeks or less but in 8 of 14 patients there was reappearance on stopping the drug Barnes considered that cortisone and ACTH should be planned to maintain suppression of the acute manifestations of rheumatic fever until its inherent duration is over as the course of the disease did not appear to be shortened Neither hormone was observed to prevent recurrence nor to modify pre existing chronic valvular damage and the associated cardiac hypertrophy

Dorfman and his colleagues (1950) reported a striking clinical effect on long standing rheumatic fever with ACTH therapy and that a decrease in the non specific hyaluronidase inhibitor paralleled the clinical improvement Massell and Warren (1950) later reported on 20 cases many of them severe The initial response to ACTH was impressive and pericarditis subcutaneous nodules and other rheumatic manifestations also frequently disappeared during hormone therapy Withdrawal reactions with clinical manifestations or rheumatic fever or with only a rise in the sedimentation rate were sometimes seen when hormone therapy was completed In most but not all such instances these signs subsided spontaneously over varying periods of time without any further treatment They expressed the hope that if therapy was begun early in an attack of rheumatic fever cardiac damage might be lessened or prevented

Early administration

Barnes (1951) has concluded that the effect of these hormones on rheumatic fever depends on several factors the

most important of which is early administration If the disease has been present for 3 weeks or more there may be cardiac murmurs which are not abolished If ACTH or cortisone is given early in the acute attack polyarticular symptoms elevation of temperature and increased heart rates are abolished in 1–5 days Prolonged P-R intervals decrease in a week and the sedimentation rates begin to fall This author believes that rheumatic fever has an inherent duration which varies from individual to individual and does not consider that this is shortened by the hormones He believes they may diminish or prevent chronic cardiac heart disease although as he rightly states it must be some years before it can be established that permanent cardiac damage has been prevented None of his cases showed significant elevation of blood sugar Rounding of the face was seen in several None of them developed heart failure or had an exacerbation of previously existing heart failure during treatment Kuttner and his colleagues (1951) have reported much less good results in 18 patients with severe rheumatic carditis In spite of an improvement in the general condition and subsidence of the acute carditis in the early stages of treatment there was relapse in most on withdrawal of the hormone necessitating further courses Murmurs indicative of organic heart disease were present in all 12 patients treated during the first attack 2–9 months after cessation of therapy Signs of hyperadrenalism were observed frequently but in every instance they disappeared gradually after the drug was stopped

Aronson Douglas and Lewis (1951) have reported on 2 cases of Sydenham s chorea studied during cortisone adminis tration for 2–3 weeks In neither case was the course of the disease favourably affected Wilson and Helper (1950) have studied the effect of ACTH given in normal dosage over the short period of 1 week in acute rheumatic carditis and have followed these patients for some months afterwards They conclude from their observations that during the acute exuda tive phase—oedema and swelling of the ground substance accumulation of inflammatory cells and increased capillary

gallop rhythm which was suppressed by a further month s treatment at a lower dosage Barnes (1950) studied acute rheumatic fever during the first attack in 10 cases 7 were treated with cortisone and 3 with ACTH Cardiac enlargement was not seen after discharge from hospital for a period of 10 months but 5 patients had developed apical systolic murmurs In patients studied during recurring attacks of acute rheumatic fever there was reduction in cardiac size during cortisone administration He concluded that cortisone and ACTH can suppress the acute manifestations of the disease in 3 weeks or less but in 8 of 14 patients there was reappearance on stopping the drug Barnes considered that cortisone and ACTH should be planned to maintain suppression of the acute mani festations of rheumatic fever until its inherent duration is over as the course of the disease did not appear to be shortened Neither hormone was observed to prevent recurrence nor to modify pre existing chronic valvular damage and the asso ciated cardiac hypertrophy

Dorfman and his colleagues (1950) reported a striking clinical effect on long standing rheumatic fever with ACTH therapy and that a decrease in the non specific hyaluronidase inhibitor paralleled the clinical improvement Massell and Warren (1950) later reported on 20 cases many of them severe The initial response to ACTH was impressive and pericarditis subcutaneous nodules and other rheumatic manifestations also frequently disappeared during hormone therapy Withdrawal reactions with clinical manifestations or rheumatic fever or with only a rise in the sedimentation rate were sometimes seen when hormone therapy was completed In most but not all such instances these signs subsided spontaneously over varying periods of time without any further treatment They expressed the hope that if therapy was begun early in an attack of rheumatic fever cardiac damage might be lessened or prevented

Early administration

Barnes (1951) has concluded that the effect of these hor mones on rheumatic fever depends on several factors the

meagre supplies of the hormones at that time and pointed out that their study was offered as an investigation of the physio logical effects in rheumatoid arthritis The therapeutic implications were specifically avoided

The antecedent work which led to the trial of cortisone in rheumatoid arthritis was embodied in the report Improve ment in this disease during jaundice and pregnancy had suggested the existence of an anti rheumatic substance X possibly an adrenal hormone The authors stated that their interest in Kendall s compound E was recorded in January 1941 The difficulty of its production made supplies so scarce that none was available for trial at that time By a combined effort of considerable magnitude the chemists of the Mayo Clinic and of Merck & Co Inc evolved a method of partial synthesis with an improved yield and supplies were made available for study in 1948

It soon became obvious that these hormones had a striking effect in rheumatoid arthritis and the Mayo Clinic invited 5 physicians who were known to be extremely critical of any claims for the successful treatment of rheumatoid arthritis to see the investigations and each was given sufficient cortisone to treat 1 case under their own control One of the most dramatic moments at the International Congress of Rheumatic Diseases in New York in June 1949 was when after Hench and Kendall had read their papers on this subject these 5 physicians one after another confirmed the effects of this drug in their own cases After the Congress we were able with many other physicians to go to the Mayo Clinic and see this work and were shown cases of rheumatoid arthritis before and after administration of these drugs During 1949 there were a few reports from other centres in the United States of America on small numbers of patients with rheumatoid arthritis These confirmed the findings of the Mayo Clinic group both with regard to the effects of the hormones and the prompt relapse when they were withdrawn In the following years many larger series treated for long periods were reported from the United States

permeability—treatment results in termination of the acute inflammatory process

Bywaters and Dixon (1952) studied these hormones in cases of acute rheumatic fever They report that they cannot regard the hormones as other than powerful and expensive suppressive agents which like other powerful remedies can also produce severe and undesirable disturbances of the body s equilibrium They conclude that the suppressive action in rheumatic fever in childhood is similar to but rather more powerful than that of the salicylates

As has been seen from the above there is yet no answer to the vexed question as to whether cortisone and ACTH are much superior to salicylates in the treatment of rheumatic fever

In an attempt to answer this the Medical Research Councils of the United States of America Canada and Great Britain are undertaking joint trials at selected centres in each country and it is hoped that their results will furnish definite evidence on this point within 1–2 years

RHEUMATOID ARTHRITIS

Introduction of cortisone and ACTH

In the spring of 1949 Hench Kendall Slocumb and Polley of the Mayo Clinic reported on The effect of a hormone of the adrenal cortex (17 hydroxy 11 dehydro corticosterone (compound E)) and of pituitary adrenocorticotropic hormone on rheumatoid arthritis In this article the remarkable effects of compound E (cortisone) and ACTH on the course of rheumatoid arthritis were announced for the first time This preliminary report embodied the results of 6 months experience of the effects observed in 14 patients who received cortisone for varying periods 2 of these patients also received ACTH It bluntly announced at the beginning that in every case improvement in clinical features and in the erythrocyte sedimentation rate began within a few days Prompt relapse generally followed withdrawal of the hormone Results were essentially similar with ACTH The authors stressed the

cases assessment of joint tenderness and range of movement and functional tests such as walking climbing stairs putting on a coat and mounting a chair

These steroids were used by intramuscular injection and an inert material (cholesterol) was used as a control The clinical results were uniformly negative however

Clinical effect in rheumatoid arthritis

The clinical response to cortisone and ACTH is similar and if the original dose schedule used by Hench and his colleagues in 1949 is followed with cortisone 300 milligrams on the first day 200 milligrams on the second and 100 milli grams on succeeding days will be dramatic in almost every case unless there is extensive permanent joint damage Janus (1950) has evolved sensitive and reliable methods for studying some of the features of rheumatoid arthritis such as joint blood flow and finger tip skin temperature and has shown that in suitable patients a response to a single dose of cortisone and ACTH can be measured The first component of rheumatoid arthritis to be affected is stiffness and the first patient treated at the Mayo Clinic (in June 1949) observed I feel as if my limbs have been unlocked This often occurs within a few hours and always in 1–2 days and is quickly followed by relief of pain with a marked fall in the amount of analgesic required One of the early effects noted with relief by the patients is that they can sleep through the night without being woken with pain Soon afterwards usually within a day or so on high initial dosage patients with rheumatoid arthritis on cortisone or ACTH find they can achieve certain movements that may have been too painful to carry out for a long time One of the authors early cases who had been unable to hold a cup of tea could hold a pot with 1 hand on the second day another who had been bedridden could get out of bed alone on the third day and a third who had been unable to take a bath unaided for 2 years could do so on the eighth day This increased mobility is striking both to the patients and observers and a woman who had been unable to jump at all could do so 40 times in a minute by the tenth day

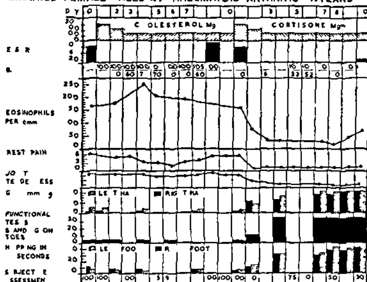


FIG 2 —Clinical effects of cortisone in rheumatoid arthritis in a short trial comparing it with injections of an inert substance (cholesterol) (*By courtesy of the British Medical Journal*)

During 1950 a small supply of cortisone was made available in Great Britain and it became possible to undertake the first European clinical trial of cortisone in 5 patients with active rheumatoid arthritis for a period of 10 days each (Copeman and his colleagues 1950) The results showed clearly the clinical effects of the hormone even over such a short period as 10 days Since then selected cases of rheumatoid arthritis have been studied for longer periods on continuous administration (Copeman and his colleagues 1952)

Other steroids

During the previous year this group had carried out trials of other available steroids in this disease in which it is notoriously difficult to assess improvement as has been pointed out by Quin, Mason and Knowelden (1950) Criteria used in assessing the results were recorded interviews before during and after treatment filming of certain movements in selected

improvement in the joint condition there is also a response in the general features of rheumatoid arthritis Fever and tachycardia subside and the lassitude which is such a feature of this disease is abolished Instead the patients exhibit euphoria and it is often difficult to be sure how much of this is due to relief of pain and how much to the action of the hormone Because of this euphoria it may be difficult to assess the degree of improvement and show the importance of the careful assessment of tenderness joint movement and simple functional tests such as the strength of the grip (measured by a blood pressure apparatus) and the ability to perform simple timed functions such as walking a measured distance or raising the arms a certain number of times These assess ments are of particular value when the dose is to be lowered to a maintenance level for then the patient fearful of a relapse may over emphasize any discomfort and this can be checked by tests such as those mentioned above In general it is important to choose the tests individually according to the patient s particular disabilities No single quota of tests can possibly be satisfactory if indiscriminately used In addition to the feeling of general well being there is an increase in appetite which may become voracious and even in the absence of evidence of sodium retention there is a gain in weight in most cases

ACTH produces the same effects as cortisone in active rheumatoid arthritis With high initial dosage the results are dramatic and with lower doses more gradual The schedule we have found satisfactory for the early stages of adminis tration is 80–100 milligrams each day split into 4 injections There is not only adequate confirmation from very many sources of the effect of these hormones on the clinical aspects of rheumatoid arthritis but also that on withdrawal of the drugs there is almost immediate relapse of the arthritis to its former activity or even an increased activity If the hormone is stopped suddenly without a gradual reduction in dosage there are in addition severe effects comprising asthenia severe depression and even circulatory collapse but even with

However such dramatic results on the high initial dosage are not entirely to be desired when one is planning what may have to be an indefinite period of administration of these drugs in rheumatoid arthritis The patient is often disappointed that the improvement is not continued at the same rate when the dosage has to be lowered to a maintenance level and there is a real danger that in attempting to perform movements that have been denied them for months or years they may strain muscles weakened by the disease We have had a number of sprained ankles in patients who have attempted to walk too fast too soon a snapped finger tendon after a vigorous trial of hand movements and an early case who had been unable previously to leave her house tripped and broke her nose on her first outing

Because of this we now prefer to avoid the dramatic response achieved by the high initial dosage and recommend 100 milli grams a day in divided oral dosage at the beginning On this schedule there is a slower improvement and it is usually 5–7 days before the patient notices any marked relief We continue with this dosage until the patient is comfortable Boland and Headley (1951) found that cortisone by the mouth was highly effective in surpressing the activity of rheumatoid arthritis in 22 of 23 cases and Ward and his colleagues (1951) that oral administration was comparable to intramuscular injection in 99 to 100 cases

Joint tenderness disappears slightly more slowly than pain and reduction in articular swelling is usually slower in appear ing and may not be complete Sometimes swelling and effusion disappear rapidly and completely Within a few weeks mild flexion deformities of the elbows and knee joints may be corrected muscle strength returns more slowly In severe and long standing cases swelling and effusion particularly of the knee joints may persist in spite of prolonged administration but they are usually painless It must be realized from the outset both by the patient and the physician that destructive deformities and ligamentous calcification are not altered by these hormones however large a dose is given As well as the

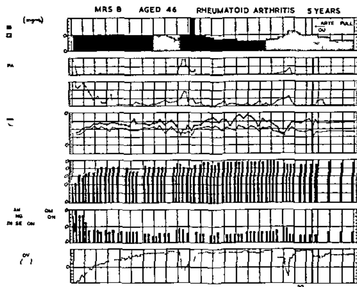


FIG 3 —Cortisone therapy Low initial dosage Relapse at ninth week when oral dose was reduced too quickly and slight relapse at nineteenth week after changing to oral therapy in insufficient dosage (*By courtesy of the British Medical Journal*)

the initial course suggesting the effectiveness of the drugs does not diminish in successive courses In the authors view the great disadvantage of such a programme would be the lowering of the patient s morale by successive relapses and the fear that he may not respond to further treatment

Edstrom (1949) has attempted pituitary implantation in a series of cases and was reasonably impressed with this though the rise in 17 ketosteroid excretion in each case was short lived

Thorn (1951) has pointed out that an intravenous infusion of 20 milligrams of ACTH in glucose lasting 8 hours or more produces a physiologic response equal to 200 milligrams of intramuscular ACTH given intermittently This method has been tried in the hope of some lasting benefit but the relapse has in most cases been rapid and did not prove of practical benefit *in the management of rheumatoid arthritis (West* London Hospital Report 1953)

gradual withdrawal the disease relapses almost inevitably within a few weeks to its former activity There is no evidence up to date that either hormone affects the length of activity of rheumatoid arthritis though they suppress it while they are being given In some series of published cases 1 or 2 patients have retained their improvement for some months and it seems that every now and again the onset of a remission coincides with the cessation of administration Patients respond to repeated courses of treatment in the same way as the initial course Apart from a few published exceptions most patients who respond to cortisone will react in the same way to ACTH and *vice versa* Hench has emphasized that the suppressive effect of cortisone and ACTH in rheumatoid arthritis is present only during their administration by the analogy of a fireman who wears an asbestos suit when he enters a fire So long as he wears the suit he will be protected but if he takes it off before the fire has died down he will be burnt

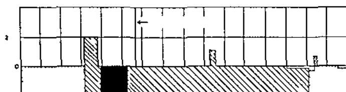
This fact raises the problem of maintenance dosage for in a chronic disease such as rheumatoid arthritis this may have to be of indefinite duration

Maintenance dosage

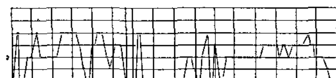
It will be seen from the previous remarks that the problem of maintenance dosage is one that has to be faced in every case of rheumatoid arthritis treated It must be assumed in every case that there will be a relapse when the drug is stopped and many methods of administration have been investigated in research centres throughout the world to try and solve this problem but so far it must be admitted without great success Hench (1950) has suggested various schemes of dosage—repeated courses alternating courses of ACTH and cortisone a combination of both hormones in short courses and indefinite maintenance dosage

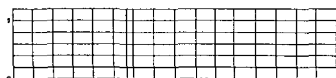
Stone Spies and Niedermeier (1950) have reported on a trial of interval therapy with ACTH and cortisone The longest remission obtained was 4½ months but they encountered minimal side effects and found that the relief of symptoms after each course of therapy was as great as that following

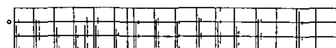
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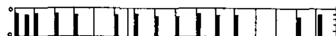














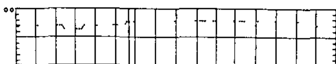


Fig 4 (*cont*)

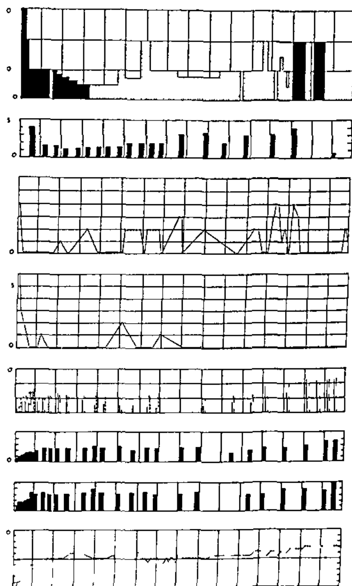


FIG 4 —Clinical response to cortisone in rheumatoid arthritis (*By courtesy of the Department of Rheumatic Diseases West London Hospital*)

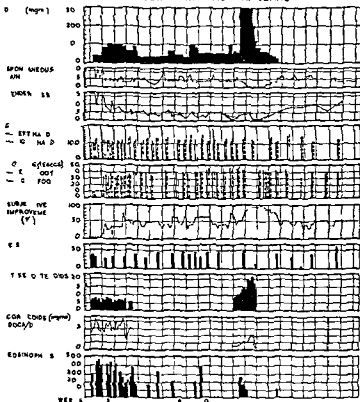


FIG 5 —Showing the clinical and metabolic responses to ACTH (*By courtesy of the Department of Rheumatic Diseases West London Hospital*)

We have had some experience of the prolonged observation of cases of rheumatoid arthritis treated with continuous cortisone (Copeman and his colleagues 1952) and ACTH for many months and a small series of cases who have had cortisone continuously for 18 months These cases were carefully selected and had suffered from active rheumatoid arthritis for at least 6 months and in most cases much longer In all of them the disease had failed to be suppressed by other measures such as rest salicylates physiotherapy and gold salts They

Boland and Headley (1950) have reported on a substantial series of cases given continuous cortisone administration for many months some for as long as 15 months and their findings are encouraging They state that as the hormone suppresses rheumatic activity but does not cure the disease it appears that if the anti rheumatic effects are to be sustained cortisone must be given continuously As these authors state much more knowledge will have to be accumulated before the answer is known as to whether prolonged dosage for years is safe and effective From their series it is evident that with careful supervision some severe cases and most less severe cases of rheumatoid arthritis may be kept under adequate clinical control for long periods with smaller maintenance doses of the hormone ranging from 32 to 65 milligrams a day providing larger doses to suppress the disease have been used initially Comparatively few unfavourable reactions were encountered and contrary to the apprehension expressed by some physicians that permanent adrenocortical atrophy would follow prolonged administration they found no evidence of this

Ward and his colleagues (1951) from their large experience at the Mayo Clinic conclude that the oral administration of cortisone in small doses unless significant side effects occur appears to be useful for the long term management of the disease

Freyberg and his colleagues (1951) investigated prolonged cortisone treatment for rheumatoid arthritis and conclude that in many patients a good partial suppression of the disease can be maintained on 75 milligrams of cortisone given each day orally Usually this amount of steroid is well tolerated and minor undesired effects can be controlled In 14 per cent of their 44 cases treatment had to be stopped because of serious side effects and they do not consider cortisone should be used on a maintenance dosage if more than 75 milligrams a day are required Relapse occurred in 83 per cent of their cases on withdrawal They conclude that cortisone should not be used as sole routine treatment for rheumatoid arthritis

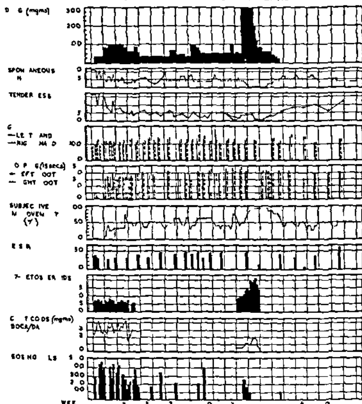


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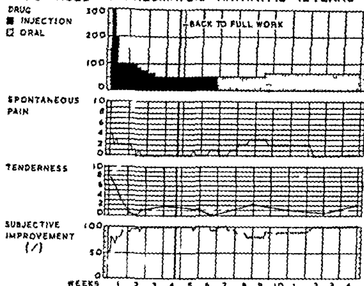


FIG 6 —Cortisone therapy Previous improvement with ACTH and relapsed to 50 per cent High initial dosage and adequate suppression of arthritis at oral maintenance dosage of 62 5 milligrams a day (*By courtesy of the British Medical Journal*)

were all regarded as severe cases since they could not carry out their normal occupations and had already become dependent on others These selected patients described themselves as crippled though since the joint changes as studied radiologically were often minimal much of their disability was potentially reversible It was emphasized to these patients that the aim from both the physician s and the patient s point of view must be to keep them comfortable and able to work on as low a dose as possible pointing out that only in this way is there any hope of eventually stopping the drug In some cases we have insisted in lowering the maintenance dose and often after a short recurrence of symptoms this has proved effective The average maintenance dose used by Copeman and his colleagues has been 50–75 milligrams of oral cortisone a day and 40–60 milligrams of ACTH

Almost all our reported cases have returned to an inde pendent life and are working many in their previous occupa tions but some in lighter ones The housewives who form the majority of the cases are able to do their housework once more though in some help has to be obtained for heavy scrubbing where kneeling is involved

The maintenance dose necessary to keep a patient comfort able varies considerably from case to case but the requirements of any single individual vary within a small range—about 25 milligrams No case has so far become refractory on prolonged administration It was also found that the dose requirements do not rise dismissing a fear expressed by some physicians in fict the maintenance doses show a tendency to fall slightly on prolonged administration

One cannot fail to be impressed with the fact that patients who have been crippled by manifestations of rheumatoid arthritis which are potentially reversible can be enabled to live an independent life once more and in most cases can earn their living on continuous administration of these hormones Whether there is danger of increasing damage to the joints or to the endocrine or other systems if this is carried on indefinitely is as yet unknown

Long-acting ACTH

A short experience of long acting ACTH has been promising and in some patients 1 injection of this preparation has lasted for 36 hours Minor side effects have occurred but in no case have they necessitated stopping either drug and they have usually been avoided by lowering the dose In only 2 cases has the disease gone into remission and in each case this was discovered by repeatedly lowering the dose until eventually complete withdrawal was effected The remission in each case is still present many months after withdrawal (West London Hospital Report 1953)

Adverse physiological effects produced by the hormones (side-effects)

It would seem appropriate to discuss these under the heading of rheumatoid arthritis for most of them have been studied

in this condition, although they also occur in the course of administration in other diseases

Cortisone and ACTH are potent hormones which, as has been pointed out are capable of influencing a wide variety of physiological functions While they exert beneficial action on certain rheumatic and other syndromes undesirable metabolic and clinical signs of adrenocortical hyperfunction may also attend their use In the early days of research with these drugs alarming reports were circulated about the undesirable side effects produced by them With further study a more rational outlook has been adopted and we agree with Hench who says they are now features generally to be respected but not greatly to be feared In most cases precautions can be taken to prevent their occurrence

Psychic changes

Definite improvement in the mental outlook of patients almost always occurs while cortisone and ACTH are being administered and sometimes an exaggerated sense of well being may develop As would be expected in a chronic disease such as rheumatoid arthritis with the fear of perma nent crippling always present dramatic relief of pain and disability generally results in a return of self confidence and often is followed by an optimistic elated mood with an accelera tion of the tempo of mental and physical activity which may be termed euphoria In most patients this is no more than a normal sense of relief when the evidence of a long standing disease has been rapidly suppressed

Rome and Braceland (1950) have observed the large number of patients with various conditions being investigated at the Mayo Clinic and divide the patient s psychiatric responses into 4 groups

(1) Those who express their relief in being free from pain often for the first time for months or years and in the lessening of disability obtain a rejuvenated hope of living a normal life once more This is the reaction seen in the vast majority of patients

(2) Those who in addition to the relief from fear of being crippled show an elaboration of stimulation and some degree of exhibitionism Such patients are anxious to show everyone they meet the extraordinary effect of these drugs and tend to tire themselves by testing their new powers of performance An example of this was seen in a girl with rheumatoid arthritis who had been unable to have a bath by herself for many months When she was able to do this she had six baths in one day as she said to make sure I could really do it

(3) Those who have a history of previous psychological conflict and may have experienced mild hypomania or mild depression or both before the onset of treatment In this group previous personality disorders may be exacerbated by the hormones and such patients may develop phobias or ritualistic behaviour They suffer particularly from moods of fearfulness lest they may cease to respond to the hormones

(4) A small group composed of patients with a pre psychotic personality Periods of psychosis have been seen in some of this group particularly in diseases in which psychosis may occur

Thus it is important that a careful evaluation of the patient s personality and family history should be carried out where the use of these hormones is contemplated and if there is a pos sibility of psychosis they should be withheld

The authors and their colleagues have not encountered any psychosis in their series but have been careful to select cases with mental stability for long term administration Some patients complained temporarily of slight exhaustion and apathy and occasionally a feeling of quick temper and tension has been noted on high dosage There has been an absence of euphoria and in no case has insomnia been a prominent symptom Some patients have complained of transient morning headaches

Sodium and water retention

Although cortisone and ACTH have comparatively weak electrolytic activity compared with other adrenal steroids such as desoxycorticosterone and compound S they can cause

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It has been recommended that this be treated by administering extra potassium in the form of either the chloride or the nitrate in a dosage of 1 gramme up to 15 grammes a day by mouth

Hyperglycaemia

Physiological studies have shown that cortisone and ACTH exert their main effect on carbohydrate metabolism and that they will produce hyperglycaemia in force fed rats In Addison s disease cortisone has been found to lessen the sensitivity to insulin and to intensify hyperglycaemia The glycogen storage in the liver has been shown to be increased This animal work has emphasized the possibility of the hormones producing a diabetic state in susceptible patients However Ingle (1950) has reported that in animals this effect may not be sustained throughout prolonged administration and that the normal animal is capable of adaptation to a continued diabetogenic dose and that glycosuria may disappear The amounts of the drugs used to induce frank diabetes in rats are many times greater for their relative weight than those used therapeutically in man It has been suggested that apart from the effect on carbohydrate metabolism there may be 2 other mechanisms which play a part in producing glycosuria when these hormones are used a deficiency of the insulin producing mechanism and a lowering of the renal threshold for sugar and it has been reported (Conn Louis and Wheeler 1948 Sprague and his colleagues 1950) that pronounced glycosuria has been found with only mild hyperglycaemia In view of these effects of cortisone and ACTH precautions must be taken to exclude abnormal carbohydrate metabolism in patients with rheumatoid arthritis in whom administration is contemplated This must be done particularly where there is a family history of diabetes It is our routine to enquire particularly on this point and if there is any likelihood of a pre diabetic state being present to do a carbohydrate tolerance test The urine should be tested for sugar before and during treatment as a routine Cases of rheumatoid arthritis and diabetes have been successfully treated with cortisone and ACTH where the severity of the joint

sufficient retention of sodium chloride and water on occasions to cause oedema We have seen this to a minor degree during the early stage of hormone administration particularly on high dosage and subsidence of the oedema later without change of dose The matter has been clarified by the work of Sprague and his colleagues (1950) who found in balance studies that there was a prompt retention of sodium and chloride during the first few days on these drugs followed by increased excretion so that the balances became negative while the hormones were still being given Levitt and Bader (1951) have carried out water metabolism studies by deter mining the inulin space distribution during administration of cortisone and ACTH Their work suggests that the hormones produce a transient but significant shift of water sodium and chloride into the measurable extracellular space From the clinical aspect this condition usually adjusts itself by a brisk diuresis after about 7 days but it may complicate treatment if high dosage has to be continued for a prolonged period The water retention can be detected if a careful watch is kept for any rapid gain in weight or for the presence of oedema which occurs most commonly round the ankles or in the pre tibial area but in severe cases may be seen as ascites and hepatic or pulmonary congestion This fluid retention can usually be controlled by restricting the salt intake and if prolonged high dosage is contemplated this should be main tained at less than 1 gramme daily with restriction of fluid intake in addition If these measures do not suffice then mercurial diuretics can be used as long as there is no renal damage present

Potassium deficiency

In balance studies cortisone and ACTH have been shown to cause increased excretion of potassium This has been reported to occur during administration and manifest itself in the form of generalized weakness and the production of a metabolic alkalosis *with hiccough and motor weakness* The electrocardiogram will give evidence of hypopotassaemia by depression of T wave S T segment and the S-T junction

downy hair just below the normal hair line of the cheeks Pigmentation of the skin could possibly arise from contamination of ACTH with an anterior pituitary melanin producing hormone and it has been observed to appear rather like a prolonged bronzing from sun burn in 2 cases with continuous administration of ACTH over long periods

Other unpleasant effects

During the early days of cortisone investigations where the drug was given by injection a number of cases were seen in which deep abscess formation occurred in the buttocks following injection This danger has been removed now the drug is given by the mouth The authors saw one such abscess occur during treatment with long acting ACTH

Tuberculosis

There is evidence that tuberculosis is exacerbated by the use of these hormones Hart and Rees (1950) have reported that prior administration of cortisone to mice resulted in exacerbation of infection with Koch s bacillus and a high mortality Other workers (Spain and Molomut 1950) found that giving 5 milligrams of cortisone daily to guinea pigs 2 weeks after infection with tubercle bacilli resulted in lesions which were more widespread than in the control group For the present care should be taken to exclude present or recent tuberculous infection in patients where the use of these drugs is contemplated and any evidence of this should be regarded as an absolute contra indication to the use of either cortisone or ACTH

Peptic ulcer

It has been reported (Gray and his colleagues 1950) that these drugs cause activation of healed or quiescent peptic ulcers by increase in gastric acidity and by the concentration of pepsin in the gastric juice and that they may cause perforation and haemorrhage in peptic ulcers It is not yet known how great is the risk of ulcer activation for by now large numbers of patients both in Great Britain and in the United

condition has made this necessary and in such cases the insulin requirements rise inevitably Sprague (1951) has concluded that the effects only persist as long as the hormones are being given or for a short time afterwards If glycosuria occurs during the course of administration the dosage should be reduced, unless this is impracticable in which case it may be controlled by diet or if necessary with insulin

Abnormal deposition of fat and skin changes

Attention has been drawn to the localized thickening of the tissues of the face neck or trunk which occur in Cushing's syndrome and similar but much less pronounced effects which may appear during the administration of cortisone and ACTH The first is rounding of the face and is a common event in patients being treated with these hormones In its milder grades it is often difficult to determine whether this is merely the restoration of the normal appearance owing to the suppression of the disease and relief of pain but where it is more marked it may amount to a moon face and patients on a high dosage for prolonged periods frequently have a bloated appearance There is no doubt that as in other physiological aspects with these hormones there may be a process of adaptation to the hormones and we have observed cases with definite mooning of the face during early administration who have resumed a normal appearance without any change of dose Deposits of fat may appear in other situations and a common one is over the lower cervical and upper dorsal vertebrae where it constitutes what has been termed the buffalo hump Another place where extra fat may be prominent is the supraclavicular fossae and we have had one case in which this has been pronounced Increase of fat in the abdomen and buttocks with the occurrence of striae has also been observed Skin effects such as acne and hirsuties have been described and are presumably the result of androgenic effects of the hormones We have seen mild acne of the chin and shoulders which occurred in association with a moon face and both were eliminated by lowering the dose of cortisone Hirsuties in the authors experience has been limited to a fine growth of

his colleagues (1950) with large doses of cortisone and ACTH for long periods 61 per cent had adverse effects though most were mild Boland and Headley (1950) with 42 patients on long term administration reported 33 per cent with a dosage of 100 milligrams a day of cortisone and 8 3 per cent while a maintenance dose of 65 milligrams a day or less was given Derbes and Weiss (1951) have surveyed this particular problem in a number of diseases and conclude that the incidence of untoward reactions to cortisone and ACTH is about 8 per cent provided patients are carefully selected for treatment and dosage is judiciously determined From our own experience we would agree with this figure

There is no doubt that the number of side effects encountered in patients with rheumatoid arthritis on long term administration drops sharply when the maintenance dose is lowered to 65 milligrams a day or less and that with increasing experience of the use of these hormones the incidence of undesirable effects is becoming lower in the reports which are appearing from all over the world This is probably on account of a wider knowledge of the technique and possible complications of treatment but such effects must be watched for carefully throughout the whole course of administration of cortisone or ACTH

INFLUENCE OF THE HORMONES ON LABORATORY AND OTHER TESTS

Erythrocyte sedimentation rates

Significant decrease in the erythrocyte sedimentation rate occurs usually within a few days after cortisone and ACTH administration is started In some cases this is rapid in others it is slower Boland (1950b) has estimated that with cortisone in daily doses of 100 milligrams the rates ordinarily decrease at a speed of about 2–4 millimetres per hour from one day to the next When the dosage of the hormones is reduced to a maintenance level in rheumatoid arthritis the erythrocyte sedimentation rate rises again but levels off below the original rate (Copeman and his colleagues 1952) (Fig 2) This has

States of America have been treated with ACTH and cortisone with only a few published accounts of gastric accidents Forbes (1952) has treated patients with proved gastric ulcers with these substances to try and clarify this point and noted that with ACTH the ulcers failed to improve radiologically and that with cortisone there was healing which did not differ from healing in the control group He concludes that it is inadvisable to give ACTH to patients with active or healed gastric ulcers but it may be justifiable to administer cortisone provided that a careful watch is kept for signs of ulcer activation

Effects on bone structure

There are two important possible effects of the long term administration of these drugs in rheumatoid arthritis to which as yet we have no answer One is the effect on the joints of constant use owing to suppression of the disease which enables the patient to live an active if somewhat restricted life Serial radiological studies over many years may give the answer to this The other is the danger of osteoporosis caused by the hormones with the risk of fractures As has been mentioned the hormones may cause a negative nitrogen balance and cases of spontaneous fractures in elderly patients (Boland and Headley 1950) have been reported on prolonged cortisone therapy It has been shown that doubling the amount of protein in the diet (Pearson and Eliel 1950) can change the nitrogen balance from negative to positive during cortisone and ACTH administration and Albright (1943) has noted that testosterone can effect a positive nitrogen balance in Cushing s syndrome

Conclusion

In the early reports on series of cases of rheumatoid arthritis treated with these hormones the percentage of side effects was high though the majority were mild and did not necessitate stopping the drugs There is no doubt that adverse physiological effects are much more likely to occur in women than men and in the former those near the menopause are more liable to be affected Of 23 patients studied by Hench and

Corticosteroid and 17 ketosteroid excretion

The output of corticosteroids is increased initially when high doses of cortisone are given but with continued administration this usually declines to normal levels It is suggested that the initial increase is due to unchanged cortisone which will give the same reaction With ACTH an increase in corticoid excretion occurs and it has been found that up to half of this is hydrocortisone indicating that ACTH stimulates the adrenal cortex to produce hydrocortisone rather than cortisone itself

The excretion of 17 ketosteroids is decreased at first with the administration of cortisone and later the level rises slightly but remains below pre treatment figures in 24 hour estimations

THE PRACTICAL MANAGEMENT OF CASES OF RHEUMATOID ARTHRITIS DURING ADMINISTRATION OF CORTISONE AND ACTH

Selection of cases

It must be realized at the outset both by the physician administering these hormones and by the patient that these drugs *suppress* the disease while they are being given but apparently do not alter the course or natural history of rheumatoid arthritis Therefore if they are to be given they will certainly have to be administered for long periods of months or years and possibly indefinitely This should be made clear to the patient Because of this factor other methods of treatment should always be tried before the use of these hormones is contemplated In the majority of cases rheumatoid arthritis can be brought under control by such procedures as rest adequate splinting physiotherapy salicylates and gold salts It is ordinarily only when these measures have been given a thorough trial and failed that cortisone and ACTH should be considered However there are a number of cases in which these measures will fail and rest analgesics and physiotherapy are unable to prevent the progress of the arthritis In some patients gold salts will be found to be inadequate and even dangerous because of renal blood or skin reactions

been termed the erythrocyte sedimentation rate escape and has been noted by other workers It has been shown that there is a close relationship between the erythrocyte sedimentation rate and the level of fibrinogen in the blood and the fall in the sedimentation rate produced by cortisone and ACTH may be a non specific effect

Blood count

These drugs stimulate the haemopoietic system and it has been shown that in rheumatoid arthritis there is a reticulocyte response during the second week of administration with a rising haemoglobin and red cell count until normal levels are reached A leucocytosis usually occurs with a rise in polymorphs The level of lymphocytes may be depressed Platelets have shown an increase in some series The fall in the number of circulating eosinophils to 50 per cent or more is a well known phenomenon with ACTH and is less marked with cortisone With the former this occurs in a few hours and with the latter in a few days With prolonged administration there is an escape of these cells to a normal level in 2–4 weeks

Sensitized sheep cell agglutination (Rose's test)

This reaction which is positive in about 60 per cent of cases of active rheumatoid arthritis is usually discharged by cortisone and ACTH during the period of their administration

Joint fluid and biopsy

It has been shown (Clark Ropes and Bauer 1950) that ACTH administration in rheumatoid arthritis causes a drop in the cell count of synovial fluid The fall in cell count has also been observed as the result of intra articular hydro cortisone (Stevenson Zuckner and Freyberg 1952) After several weeks of cortisone or ACTH synovial biopsies show reduction of synovial inflammation but the synovial tissues do not appear completely to revert to normal

dosage a period of gradual reduction of dosage, and a period of minimal (maintenance) dosage

Initial suppressive dosage

When one is planning a prolonged period of treatment with these hormones it is wiser to avoid the dramatic effects which can be obtained with very high initial doses Almost all writers with experience of prolonged administration in rheumatoid arthritis are now agreed upon this point A daily oral dose of 100 milligrams of cortisone (four 25 milligram tablets or four doses of 1 millilitre of the suspension given in a vehicle to obscure the bitter taste) spread throughout the day or 80–100 milligrams of ACTH split into 4 injections will produce clinical improvement which is obvious in 5–7 days This dose is continued until the patient has improved enough to lead a comfortable life and have a reasonable prospect of returning to work This level of improvement can be assessed by the methods already described which are based on the disappearance of pain and tenderness and the performance of functional tests This stage is usually reached in 14–21 days At this point if the patient is comfortable but there seems little prospect of him returning to work because improvement has ceased we have in some cases given a boost dose of 200 milligrams a day of cortisone and 150 milligrams of ACTH every day for 10–14 days in order to gain increased improvement and to enable the patient to carry out the rehabilitation which is started at the same time as the drugs We have been impressed by the greater value of the high dosage given at this stage rather than at the outset This period of boost is not necessary in all cases and should be avoided if possible as it is during this stage that side effects such as a moon face are apt to occur

Period of gradual reduction of dosage

At a stage when the disease process is satisfactorily controlled which may be 2 or 3 weeks or longer the daily dose of cortisone is reduced by 12 5 milligrams and of ACTH by 10 milligrams at a time During this reduction we find that methods of

to the metal In such cases where the prospect of being crippled at a relatively early age is evident both to the physician and the patient the authors consider that treatment with these drugs is justified in the light of present knowledge

One other point must be made clear with regard to the selection of patients for the use of these drugs Neither *cortisone nor ACTH will affect permanent joint damage* ankylosis will not be altered and roughened joints will not be made smooth again It must be admitted that it is frequently difficult or impossible to assess how permanent flexion defor mities are and even with radiological damage present we have been surprised how much movement may sometimes be restored to deformed joints under the influence of these hormones There is no doubt however, that the use of cortisone and ACTH with their wide physiological effects is not justified merely for relief of pain in permanently crippled patients

We have learnt by experience to pay particular attention to the hip joints in this respect Fortunately rheumatoid arthritis usually leaves these unaffected but where they are damaged such high doses of cortisone and ACTH may be required that the treatment becomes difficult and occasionally impractical

Two absolute contra indications to the use of these drugs are psychosis and active or recent tuberculosis If a tendency to diabetes is present they should not be used unless it is thought that crippling from the arthritis will occur rapidly if they are withheld

Dosage

As cortisone and ACTH do not cure rheumatoid arthritis but only suppress the disease it is important that as soon as the symptoms have been relieved adequately the dose should be lowered to a level at which this improvement can be main tained for a prolonged period without the appearance of undesirable reactions The dose schedule should therefore consist of three phases a period of initial high (suppressive)

ACTH are being carried out and some substances are promising Experience of certain preparations has been gained in which one injection has been effective for 36 hours and continued to be so on repeated administration for several months up to date

Avoidance of side effects

The success of prolonged treatment with cortisone and ACTH depends to a large extent on the difference between the sup pressive dose and one that causes side effects however mild they may be This varies greatly from case to case and as yet cannot be predicted in any given case Where this margin is large administration is both simple and highly satisfactory where it is small it may be extremely difficult to achieve and maintain the balance between the control of symptoms and the incidence of undesirable effects The commonest com plication is rounding of the face and in its minor form this is not usually objectionable or at any rate the patient usually prefers it to being crippled with arthritis When it is more severe it gives rise to a bloated appearance and this is much disliked by the victims usually women near the menopause However there is no danger in this and in fact often it acts as a spur to the patient to lower the maintenance dose as it subsides when the daily amount of hormone is reduced

There is no doubt that women are more liable to have minor adverse physiological effects than men who can take much higher doses One of the minor troublesome effects in women of middle age is a rapid gain in weight without evidence of fluid retention This is partly due to the increased appetite and may have to be controlled by a lowered dose and a reducing diet as it throws an added burden on the lower limb joints Patients on cortisone and ACTH should be weighed weekly so that this tendency can be checked in its early stages Glycosuria has not proved troublesome in our experience though the urine should be tested for sugar and ketone bodies at frequent intervals If this occurs it can be controlled by a slight reduction in dosage

assessment are important as it is only in this way that the lowest maintenance dose can be found The patient knowing the dose is being reduced will be fearful of relapse and will tend to exaggerate minor changes Each reduction should be carried out at intervals of some 5–7 days and as the dose becomes lower we increase the intervals between lowering the doses The aim should be to reduce the dose of cortisone to 65 milligrams a day or less and of ACTH to 60 milligrams a day or lower and each drug should still be given in divided doses through the day

Maintenance dosage

Because the majority of cases of rheumatoid arthritis will require prolonged administration with the hormones as low a maintenance dose as possible must be found Although this may need to be increased temporarily during periods of physical and mental stress it will remain effective in most cases for prolonged periods without relapses occurring and the dose requirement tends to become lower rather than higher as time goes on It should be emphasized to the patient that the lower the dose the greater the likelihood of being able to do without the drug eventually and the patients should be encouraged to use moderate amounts of analgesics if it helps them to lower their dose requirements and repeated trials of dose reduction should be carried out throughout administration In this way there will be no severe relapses and those cases going into remission will soon become evident

In most cases the maintenance level will be found to be between 50–75 milligrams of cortisone and 30–60 milligrams of ACTH a day Some cases require much less for instance 25 milligrams of cortisone and 15 milligrams of ACTH daily and some need a higher dose It is probable that dose requirements of 100 milligrams of cortisone or 80 milligrams of ACTH or higher are not practicable for prolonged periods because of the frequent incidence of side effects at these levels

The practical difficulty with ACTH for maintenance dosage is that the substance has to be given at least three times a day by injection in order to last for 24 hours Trials with long acting

exercises and faradic foot baths should be started if possible before the hormones and certainly from the onset of treatment and foot supports may be required to correct deformities Later as the pain stiffness and tenderness in the joints is relieved the full scale of rehabilitation should be undertaken with exercises faradism to assist these if necessary and re education in walking and other movements The physio therapist must be warned that pain on movement is minimized by the drugs and care must be taken not to be too vigorous with treatment as the patients are often anxious to overdo movements themselves

Polley (1950) has emphasized the importance of the role of physical therapy once the joint stiffness and pain of rheuma toid arthritis are relieved Exercises heat and hydrotherapy can be instrumental in repairing the damage of deformed joints and wasted muscles Patients who cannot be given enough cortisone or ACTH to control the arthritis completely can be helped also by physical treatment He warns that rehabilitating exercises must be started slowly and increased gradually in order to minimize the occurrence of broken bones

In conjunction with physical medicine there may be a place for short courses of cortisone and ACTH to correct a particular deformity such as stiff shoulder or flexion deformities of the knees and elbows Restoration of movement or correction of deformity may have to be performed under anaesthesia but if this and the after treatment are covered by an umbrella of cortisone or ACTH for 3–4 weeks with a gradual withdrawal of the drug the results are often satisfactory

Other steroids and drugs to assist cortisone and ACTH

As was natural as soon as the first trials of cortisone and ACTH were announced other more easily available steroids with similar formulae were tried in rheumatoid arthritis Androstenedione dehydro iso androsterone progesterone pregnenolone pregnadienolone and 21 acetoxypregnenolone all having chemical structures resembling cortisone and hydro cortisone were tried in Great Britain (Copeman and his col leagues 1950) and an even larger number in the United States

Sodium and water retention may occur at periods of boost dosage and evidence itself by sudden increase of weight and oedema of the lower extremities It can be controlled by reduction in salt and fluid intake and by lowering the dose

Side effects are much publicized and undoubtedly occur with these hormones but we have not found much practical difficulty in dealing with them as long as the cases of rheumatoid arthritis are carefully selected and the maintenance dose is kept as low as possible

Withdrawal

If for some reason it is found impractical to continue with the administration of the hormones withdrawal must be done slowly or there is a real danger of severe and dangerous symptoms from the withdrawal syndrome This consists of asthenia depression a return of articular symptoms and occasionally circulatory collapse In any medical or surgical emergency it is extremely important that the dose of the hormone should not be lowered or the withdrawal effects will be added to those of the emergency It is probably wise to raise the dose slightly for a few days during any surgical procedure particularly if the patient has had the hormone for some time Subsequent healing is not likely to be affected by therapeutic doses

Physiotherapy

This forms an important adjunct to the treatment of rheuma toid arthritis with cortisone and ACTH Patients who may not have been able to perform functions such as dressing or even walking for months or years are capable of doing these within a few weeks under the influence of the hormones and extensive rehabilitation is required One of the disadvantages of the high initial dosage with dramatic results is that patients may attempt to do too much before rehabilitation has had time to prepare them and we have seen sprained ankles and ruptured tendons as a result of this One of the main problems is the feet and ankles which have been unused to weight bearing and may have deformities to be corrected Foot

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of America (Polley and Mason, 1950) but without effect, and it seems up to date that ACTH cortisone and hydro cortisone are unique in their effects on rheumatoid arthritis Claims have been made that a number of substances such as insulin *para* aminobenzoic acid and thyroid extract potentiate the action of cortisone but further investigation has not upheld these claims A number of investigators have suggested that gold salts given in conjunction with the hormones have pre vented relapse on withdrawal but others have denied this and the matter is at present not settled

CORTISONE AND ACTH IN OTHER RHEUMATIC DISEASES

Still's disease

Bywaters (1951) has pointed out that Still s disease differs in no way from adult rheumatoid arthritis but that certain clinical features are more common in children With cortisone as in adults the enlarged lymph nodes spleen and the arthritis fever and malaise rapidly respond and the child begins to put on weight again Remissions produced by cortisone sometimes last several weeks and he has compared these with a remission produced by intercurrent measles both are followed by relapse

Schlesinger (1952) reported a number of cases of this condi tion treated with cortisone and ACTH He reports that the same dramatic alleviation of symptoms occurs as in adult rheumatoid arthritis but the hope that the patient can be protected against crippling effects of the disease until he can take over his own disorganized defence are not justified Schlesinger has reason to suspect that the turning point of the disease may in fact be delayed by these drugs

Reiter s disease

Ogryzlo and Graham (1950) have studied the response of this rare condition characterized by arthritis urethritis and conjunctivitis in 3 cases All responded rapidly and dramati cally to ACTH and all relapsed when it was stopped Further treatment of 1 case with cortisone resulted in a more gradual

relapse on withdrawal than with ACTH They concluded that the course of the disease which is self limited was shortened by both cortisone and ACTH

Ankylosing spondylitis

In the United States of America this disease is considered to be a variant of rheumatoid arthritis and cases have been included in the various series reported and have apparently responded in the same way Boland writes that cortisone is highly effective in suppressing the activity of rheumatoid spondylitis and that most cases may be kept under satisfactory control for a long period with continued smaller maintenance doses He advocates using large initial suppressive doses followed by a gradual reduction to the smallest dose capable of upholding good but not necessarily complete symptomatic improvement He considers it should be reserved as treatment of second choice for those patients who fail to respond adequately to deep x ray therapy and general measures

Hart (1952) has studied the effect of ACTH and cortisone on ankylosing spondylitis as it is seen in Europe In his opinion while supplies are short the use of the hormones should be restricted to painful episodes He points out that most patients with this disease are at work and earning their living He has not seen the bony tenderness which is a feature of the disease relieved by these drugs as it has been by deep x ray therapy and states that the need for basic treatment of this condition in the form of postural drill and exercises has not been changed though now in ACTH and cortisone we have potent short term weapons available for more acute episodes

Osteoarthritis

Owing to the permanent nature of the bone and cartilage changes in this disease it would not be expected that cortisone and ACTH would have more than an analgesic effect As has been previously stated with regard to permanent changes in rheumatoid arthritis it is not considered that the use of hormones is justified for this purpose owing to adverse physiological effects although Boots and Ragan (1951) have

reported symptomatic relief in a small series of cases These drugs are not recommended for the treatment of osteoarthritis in the light of present knowledge

Gout

Both cortisone and ACTH have been found to cause an increase in urinary uric acid excretion and this has been used particularly in the investigation of cases of gout in which there is reported to be a miscible pool of uric acid as much as thirty times above the normal (Benedict and his colleagues 1950) It is well known that acute attacks of gout may be precipitated by various types of stress which act on adrenal cortical activity by stimulating the secretion of ACTH Hellman (1949) administered ACTH to 4 gouty subjects and precipitated acute attacks in 3 out of 5 trials, the attack beginning on the third or fourth day after injection in each He reasoned that adrenal cortical function must have reached a relatively decreased level of activity at this point and therefore administered ACTH to 2 patients in the throes of acute gout Symptoms were promptly abolished He therefore concluded that the mechanism by which stress precipitates acute gout is by stimulation of adrenal cortical function and indicated that ACTH may be a useful provocative and therapeutic agent in gout Other workers (Marjolis and Caplan 1950) observed the striking benefit obtained in severe attacks of gout with ACTH followed by colchicine Wolfson and Cohn (1950) described two types of adrenal cortical dysfunction which appear to be implicated in gout First androgen activity appears to be maintained by an abnormal cortical androgen which when metabolized contributes little to the urinary 17 ketosteroids These authors first described the low excretion of 17 ketosteroids in gout They postulate that the normal difference between plasma urate levels in the sexes is controlled by normal androgen but that gouty androgen is responsible for gouty hyperuricaemia

Secondly acute attacks of gout are they think associated with another endocrine disturbance in the regulation of corticosteroid secretion by the adrenal cortex leading to a

relative deficiency An acute attack of gout appears to be terminated by an increase in the level of corticosteroids and may be induced by ACTH Thus in gouty patients ACTH given in an interval of freedom and then withdrawn will precipitate an acute attack but given in an acute attack it will rapidly relieve it and if colchicine is given concurrently then the relapse on withdrawal of ACTH will be prevented There does not seem to be any relation between the effect of ACTH and the level of plasma uric acid

At the moment there does not seem to be any advantage in cortisone and ACTH in the practical therapeutics of gout save perhaps in rare cases which are completely resistant to colchicine

"Fibrositis

Cortisone and ACTH have been little used for the relatively mild but varying syndromes which come under this heading Ehrlich and his colleagues (1951) have reported on a few cases of frozen shoulder many of which were greatly improved following administration of the hormones which were continued as a maintenance dose for a limited time A small series (Sigler and Ensign 1951) of the shoulder hand syndrome have also been favourably reported on with improvement without relapse on withdrawal Shuman (1951) has reported a case of relapsing panniculitis (Weber Christian disease) which had failed to respond to antibiotics x rays therapy and other methods and was rendered afebrile with cortisone but relapsed on withdrawal

CORTISONE AND ACTH IN OTHER COLLAGEN DISEASES

Disseminated lupus erythematosus

A number of studies have been reported on the effects of the hormones in this rare condition and it is difficult to assess their significance The total of cases reported is small and it has been realized in recent years that this disease with its multiple manifestations including rheumatic pain and arthritis fever anaemia polyserositis endocarditis and nephritis is not always

fatal as was formerly supposed From a report of 9 cases (Johnson and Meyer 1952) it is concluded that cortisone administration is usually effective in the amelioration of symptoms and signs of the disease but relapse follows cessation of therapy and that it probably has its chief value in the treatment of acute episodes where it may tide the patient over a critical period and may be life saving Tumulty and McGehee Harvey (1952) reviewing the response to the hormones in this disease point out that although they have a profound effect on many of the acute manifestations an occasional patient with lupus fails to respond There is a group of patients who are made worse with these drugs and these are those with a significant degree of renal impairment due to the disease

Of a group of 18 cases (Soffer and Bader 1952) treated with a high dosage of cortisone and ACTH for periods of 3–20 months 6 have died and 12 are living of whom 8 continue with treatment These authors point out that treatment with corticotropin or cortisone in adequate dosage causes prompt remission in fever, arthritis pleuritis Raynaud s phenomenon and the organic mental syndrome The rash mucous membrane lesions retinal lesions and serous effusions cleared more slowly The anaemia improved slowly in those patients with minimal or no renal damage The lupus cells persisted despite a remission in the disease although at times they disappeared temporarily Renal damage was unchanged

The complications and hazards of treatment with the hormones are described and consist of congestive cardiac failure hypertension convulsions diabetes psychoses and osteoporosis These authors consider that despite the risks attendant on the use of these drugs they constitute the most effective agents yet available for the treatment of this disease although it must be emphasized that no actual cures result It is possible that some patients may be maintained in a state of remission for an indefinitely prolonged period of time with judicious treatment

Although the hormones are frequently life saving in the acute crises of this disease the attendant hazards of such therapy are considerable This is partly because a very high dosage has to

be employed to suppress the multiple manifestations and partly because of the frequency of renal involvement by the disease which constitutes an additional danger where cortisone and ACTH are employed in any condition (*see also* P 167)

Periarteritis nodosa

This condition has been included in the research programme at a number of centres because of its allergic and rheumatic manifestations and some reports have been encouraging Ragan Grokoest and Boots (1949) reported subsidence of activity of the disease with ACTH Manifestations such as purpuric rashes pruritus asthma periarteritic nodules and eosinophilia disappeared or were greatly reduced in severity but recurred when the hormone was discontinued Shick and his colleagues (1950) have reported 6 cases with 2 cases of cranial arteritis Relief of symptoms in both conditions was produced with the hormones with relapse on withdrawal The pathological lesions showed evidence of healing and in 2 patients in an advanced condition who died from cardio renal failure after cortisone had been given the arterial lesions were found to be completely healed at necropsy but the lumina of the affected vessels had become obliterated with resulting widespread infarction So far this is the only condition in which healing of the pathological lesion has been described as a result of these drugs The possibility of embolic incidents constitutes a danger to the use of the hormones in advanced cases

Dermatomyositis

Few reports of the action of these hormones have appeared and they have been limited to single cases which is natural as the condition is so rare Oppel Coker and Milhorat (1950) reported a dramatic response to ACTH in a young man seriously ill with this condition Symptoms relapsed when the dose was reduced on the seventh day but on increasing to 100 milligrams a day there was a further response and after the drug was stopped on the fifty third day there was no relapse during an observation period of 2 months

Thorn and his colleagues (1950) report 3 cases and express the opinion that ACTH can alter the acute inflammatory and destructive process within the affected muscles but do not consider that a lasting remission is likely to be obtained except with vigorous treatment in the very early cases

Suzman and Rudolph (1951) reported a case from South Africa in which there had been no benefit from treatment with sulphonamides salicylates, penicillin aureomycin pregnenolone or deoxycortone or testosterone in combination with ascorbic acid Prompt and dramatic improvement followed the admin istration of ACTH in the initial daily dosage of 40 milligrams for 15 days Recovery ensued after the patient had received 860 milligrams of ACTH in 99 days and there was no relapse in a 14 week follow up Williams and Bowler (1951) report a case in which the arrest of the disease was still evident 9 months after treatment with small doses of ACTH (*see also* P 186)

Scleroderma

The response of this condition to cortisone and ACTH has been studied and a few reports published Bayles and his colleagues (1950) treated 4 cases with ACTH and observed some improvement during administration but complete relapse on withdrawal There was increase of appetite relief of joint pain and loosening of the skin which felt warmer but skin biopsy showed no notable histological improvement Hines and his colleagues (1950) studied the peripheral circulation and blood pressure in 3 cases following the administration of corti sone The blood flow in the forearms and legs as measured with a plethysmograph showed a gradual but slight increase lasting more than 90 minutes after the administration of 100 milli grams of cortisone 300 milligrams gave a similar but no greater effect There was no change in skin temperature or blood pressure after 300 or 100 milligrams of cortisone or 100 milligrams of ACTH Taubenhaus and Lev (1951) report a case treated with cortisone for nearly a year with improvement in the symptoms and the collagen pattern while others (Sharn off Candeo and Stein 1951) report a case with initial dramatic

improvement followed by hypertensive encephalopathy and death in uraemia (*see also* P 189)

HYDROCORTISONE (COMPOUND F)

Kendall s compound F (17 hydroxycorticosterone) has been re named hydrocortisone and has been known for some time to have anti rheumatic activity and to be physiologically at least as active as cortisone Fourman and his colleagues (1950) noted its effect in a normal man by giving injections of 50 milligrams for 3 days and observed a fall of eosinophils and lymphocytes and a loss of potassium and nitrogen similar to that obtained with ACTH Conn Louis and Fajans (1951) produced further evidence that hydrocortisone is the hormone produced by the normal human adrenal cortex by studying the effects of ingestion of 400 milligrams a day and observing the same metabolic changes as were produced by ACTH Boland (1952) has studied the effects of hydrocortisone (free alcohol) and hydrocortisone acetate in rheumatoid arthritis and compared them with cortisone (free alcohol) He found that hydro cortisone (free alcohol) milligram for milligram was 50 per cent more potent than cortisone and twice as effective as hydrocortisone acetate As he states his numbers were small but it seemed that the increased anti rheumatic effect was not accompanied by a correspondingly greater increase of adverse effects in fact those patients with mild side effects on cortisone lost these when transferred to a lower dose of hydrocortisone with the same anti rheumatic activity and in no case did new effects occur

Most of the work so far reported has been with hydro cortisone used for intra articular injections Hollander and his colleagues (1951) have compared the results of intra articular cortisone and hydrocortisone They found that with 25 milligrams of cortisone there was no marked reduction in synovial cell count and no change in intra articular tempera ture With 25 milligrams of hydrocortisone injected into the knee joints there was a significant improvement in swelling tenderness and freedom of movement and a reduction of

50 per cent in the cell count of the synovial fluid The intra articular temperature was markedly decreased The improve ment in the joint condition varied from a few days to a few weeks and was longer in osteoarthritis of the knees Repeated injections have been equally effective and no adverse effects occurred These results have been confirmed by Stevenson and his colleagues (1952) who found a substantial reduction in the synovial cell count and particularly in the polymorphs in knee joints of patients with rheumatoid arthritis which lasted some 14 days Results were better when all available joint fluid was aspirated before the injection There was no improvement apart from the local joint change though the sedimentation rate fell in some instances Kersley and Desmarais (1952) have confirmed these results in Great Britain

It seems that in hydrocortisone we may have a more potent weapon both for systemic and local treatment and the finding of Boland that the adverse physiological effects are less is particularly encouraging at present however this hormone remains in short supply

CONCLUSION

The first clinical effects reported with cortisone and ACTH were in rheumatoid arthritis although subsequently these sub stances have been used in a host of different diseases It seems at the moment that they will always have a practical part to play in the treatment of those cases of rheumatoid arthritis where the progress of the disease cannot be checked by other methods It has proved disappointing to find however that even with variations in dosage and methods of administration the vast majority of patients relapse soon after either hormone is with drawn The small supplies available in Great Britain have increased the practical difficulties of dealing with cases where it had not been realized that once a patient with rheumatoid arthritis is started on cortisone or ACTH supplies must be a lo cated for very prolonged or indefinite treatment The dramatic effects of high dosage have been abundantly confirmed but the attention of investigators during the last 2 years has been

focused on avoiding these and of finding a practical method of administering the hormones over long periods with the avoid ance of side effects and there is evidence from a number of reports that with increasing experience considerable progress has been made towards solving this problem The emphasis on immediate side effects has lessened and the fear of adverse changes from long term administration is becoming smaller as more patients are followed on such a regime without the occurrence of catastrophes Further improvements in methods of long term administration of cortisone and ACTH will undoubtedly occur particularly in the production of longer acting ACTH and one can visualize the time not far ahead when patients with rheumatoid arthritis may require an injection of ACTH only once a week which would considerably relieve the supply problem which is at present one of the main practical difficulties of treatment

The reports of the increased anti arthritic action both systemic and local of hydrocortisone and the lower proportion of adverse effects resulting from its use are most encouraging

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CHAPTER 2

DISEASES OF THE EYE

EXPERIMENTAL AND THEORETICAL CONSIDERATIONS

Tolerance

General administration

Cortisone or ACTH administered by the various systemic routes gives no ocular reactions of intolerance so that only the general side effects need to be considered in dosage for systemic use

Topical applications

Cortisone used locally is well tolerated

Drops—The ordinary commercial preparation which contains 25 milligrams per millilitre carries benzyl alcohol as a preservative and this itself is irritating to the eye Dilutions of 1 4 with normal saline solution are necessary to produce a non irritant suspension If however Zephiran 1 5 000 is used as a preservative the full concentration can be employed A suspension for ophthalmic use in a buffered phosphate solution with this preservative is now available

Ointment—Concentrations of 25 milligrams per gramme in a non irritating base are well tolerated A simple base such as lanolin is probably best

Subconjunctival injections—Injections of the ordinary commercial preparation are well tolerated Doses of 1 millilitre containing 25 milligrams are borne without much discomfort There is frequently a small subconjunctival haemorrhage at the site of injection and within 12–24 hours the cortisone shows as a yellowish white deposit beneath the conjunctiva Absorption of this deposit takes 5-7 days

Retrobulbar injection—Experience with this method is limited Leopold and his associates (1951) report severe local

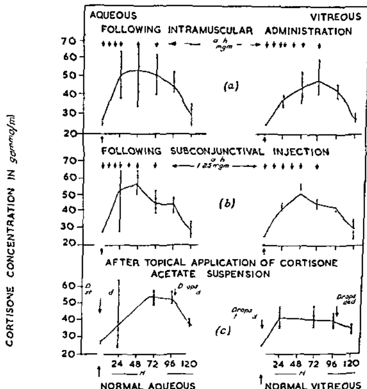


FIG 7—Comparative levels of concentration of cortisone reached by different methods of administration (*after Leopold and Maylath*) (*By courtesy of the American Journal of Ophthalmology*)

reactions on injecting 50 milligrams of cortisone in 2 millilitres of suspension with 0 5 millilitre of 4 per cent cocaine in the fluid The reactions may be so severe as to simulate a retro bulbar abscess without systemic manifestations

Levels of concentration

A satisfactory assessment of the levels of concentration of cortisone in the ocular tissues is as yet impossible for there is no method of assay which specifically determines the presence of cortisone as distinct from corticoid substances some normally present Leopold and Maylath (1952) using the test devised

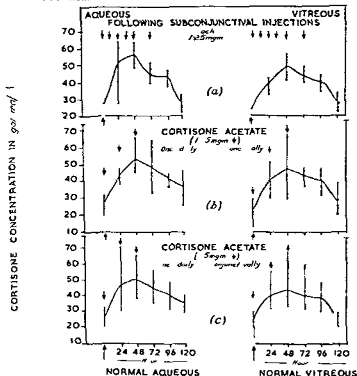


FIG 8—Levels reached by subconjunctival injections of various concentrations (*after Leopold and Maylath*) (*By courtesy of the American Journal of Ophthalmology*)

by Porter and Silber established for the aqueous and vitreous of the rabbit comparative values as to the different routes of administration

Intramuscular injection at frequent intervals

Intramuscular cortisone was given in the following dosage 100 milligrams 3 times a day for the first day at 8 hourly intervals twice the next day at 12 hourly intervals and 1 daily injection for the next 2 days

Peak levels were obtained in the aqueous within 24 hours and were well maintained for 72 hours Thereafter there was

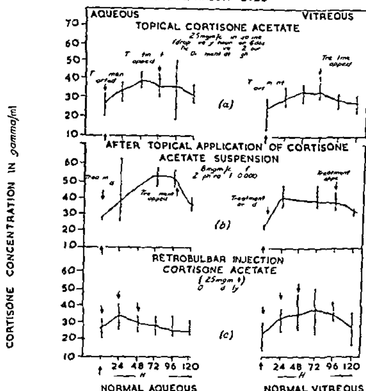


FIG 9—Levels reached by cortisone drops in saline or Zephiran suspension or by retrobulbar injection (*after Leopold and Maylath*) (*By courtesy of the American Journal of Ophthalmology*)

a rapid decline so that within 24 hours after the last intra muscular injection the concentrations approximated those of the normal rabbit aqueous The concentrations obtained in the vitreous were on a somewhat lower level but followed very much the same pattern

Subconjunctival injection

Repeated small doses—This method was carried out with 1 25 milligrams twice daily for 48 hours and once daily for the next 48 hours A higher average level was reached than with systemic injections Peak levels were obtained within

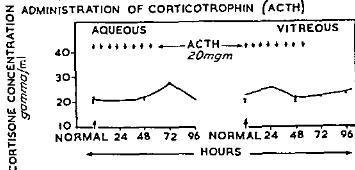


FIG 10 —Levels of concentrations after intramuscular injection of ACTH (*after Leopold and Maylath*) (*By courtesy of the American Journal of Ophthalmology*)

24–48 hours but tended to fall off rather rapidly thereafter As with intramuscular injections the levels in the vitreous were rather lower

Standard clinical dose —With 12 5 milligrams once daily subconjunctivally for 3 days there was no increase in the level of concentration reached in the aqueous and vitreous by repeated small doses but these levels did not fall so rapidly on suspension of treatment

More massive doses —Injection of 25 milligrams given once daily for 3 days did not materially increase either concentration or persistence in both aqueous and vitreous as compared with the levels obtained with doses of 12 5 milligrams

The levels reached in the aqueous and vitreous following injection by the intramuscular route and by subconjunctival injection of repeated small doses are shown in Fig 7 *a* and *b* Fig 8 shows the comparative levels reached with the different doses and frequency of administration with subconjunctival injection It appears that subconjunctival injections in adequate dosage give aqueous and vitreous levels of the same order as obtained with systemic administration

Instillation of drops at frequent intervals

Cortisone acetate suspension diluted 1 4 in Zephiran (1 10 000) was instilled every hour for 6 hours and then

4 times at 2 hourly intervals, 2 hourly instillations were then given 4 times a day for 4 days

The levels obtained by this procedure are shown in Fig 7 *c* Compared with systemic and subconjunctival injections there was some delay in reaching peak levels and these dropped rapidly on suspension of treatment The levels in the aqueous were not substantially different from those obtained by the other methods, but the levels in the vitreous were distinctly lower

The nature of the suspension used as drops greatly affected the levels that could be obtained This is shown graphically in Fig 9 *a* and *b* Drops containing 8 milligrams per millilitre of cortisone suspension in Zephiran 1 10 000 gave higher levels in both aqueous and vitreous than drops containing 25 milligrams per millilitre in saline solution

Retrobulbar injection

With injections of 25 milligrams once daily for 3 days both the aqueous levels and the vitreous levels were low, and showed little persistence (Fig 9 *c*)

Systemic injection of ACTH

In the experimental rabbit intramuscular administration of ACTH produced no substantial or persistent levels of cortisone in the anterior chamber or vitreous (Fig 10) Intravenous injections were no more effective

Effects on tissues

The acute inflammatory reaction

The striking effect of cortisone on the acute inflammatory process is well seen in the eye of the experimental animal The simplest form of inflammatory reaction is that obtained as the response of a sensitized tissue to a specific irritant In studies on uveitis produced in sensitized rabbits by injecting horse serum into the vitreous Biegel (1951) was able to compare the inflammatory reaction observed in control rabbits against those seen in rabbits previously treated with cortisone

intramuscularly There was marked inhibition of inflammatory exudate in the treated rabbits Other observers have recorded similar effects of cortisone on the inflammatory reaction produced by dead streptococci and by dead tubercle bacilli in sensitized rabbits Likewise cortisone controls the inflammatory process induced by such irritants as jequirity alloxan talc or by thermal injuries

The acute inflammatory process in relation to infection and to repair

Since the inflammatory reaction is a defensive response to infection and also an essential aspect of the process of repair in a tissue the inhibitory effect of cortisone on the inflammation raises the fundamental question as to whether cortisone is beneficient clinically

Infection—The studies of Woods and Wood (1950) have shown that the use of cortisone in rabbits with artificially induced tuberculous lesions leads to the paradoxical condition of white non inflamed eyes with active tuberculosis Rabbits that were immune allergic to tuberculosis showed relatively limited reactions to the tubercle bacillus (in contrast to the widespread destructive processes seen in the non immune rabbit) but the administration of cortisone precipitated in such animals the same destructive reaction as was seen in the non immune rabbits (Figs 11–13) Similar results have been obtained in general infections with the staphylococcus, and there is evidence that cortisone facilitates the development of other generalized infections

Repair—In general pathology there is considerable evidence that there is retardation of wound healing with the use of cortisone This would however appear to be a relative rather than an absolute effect for much depends upon dosage and with the dosages in clinical use there is apparently no deleterious effect From experimental studies on wounds of the cornea it appears that there is little interference with epithelialization and repair of the stroma but considerable delay in endothelial proliferation (Newell and Dixon 1951 Ashton and Cook 1951) Parallel and possibly related to the



FIG 11 —Ocular tuberculosis in untreated normal control (*a*) globe showing buphthalmos and rupture of globe 60 days after inoculation (*b*) iris showing necrosis and caseous tubercles 60 days after inoculation (*By courtesy of the British Journal of Ophthalmology*)

(*a*)



(*b*)

interference with endothelial proliferation is the inhibition of new vessel formation in corneal wounds—an inhibition seen strikingly in experimental thermal and caustic injuries of the

Fig 12—Ocular tuberculosis in untreated immune allergic control (*a*) globe showing restrained healing tubercles of iris 90 days after inoculation (*b*) iris showing nondescript granulomatous lesion 90 days after inoculation (*By courtesy of the British Journal of Ophthalmology*)



(*a*)



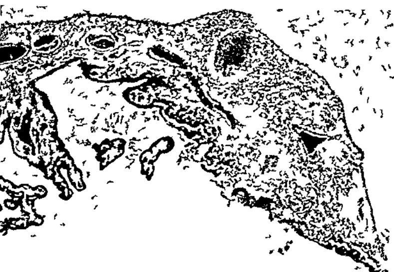
(*b*)

cornea (Jones and Meyer 1950 Lister and Greaves 1951 Leopold and Maylath 1952) and in the vascularization precipitated in the cornea by injection of alloxan into the anterior chamber (Ashton Cook and Langham 1951)



FIG 11.—Ocular tuberculosis in untreated normal control (*a*) globe showing buphthalmos and rupture of globe 60 days after inoculation (*b*) iris showing necrosis and caseous tubercles 60 days after inoculation (*By courtesy of the British Journal of Ophthalmology*.)

(*a*)



(*b*)

interference with endothelial proliferation is the inhibition of new vessel formation in corneal wounds—an inhibition seen strikingly in experimental thermal and caustic injuries of the

clinically The actual levels of concentration that can be reached with the different methods of administration still remain to be determined as do possibilities for increasing such levels by adjuvants Until the different effects of cortisone are better known it is difficult to establish a dosage that would give a clinically desirable result without undesirable local effects (as distinct from general disturbances)

Inflammatory conditions

The inhibition of an acute inflammatory reaction may in some individual affections be the major clinical problem and in such cases the indication for the use of cortisone is clear It follows that in any self limiting acute inflammatory reaction cortisone therapy has a definite place if the inflammatory reaction itself carries serious sequelae An extreme and clinically rather unusual situation would be an acute iritis with massive exudation tending to block the pupil and not responding to effective mydriatic treatment

Cortisone has an obvious place in the treatment of the sympathizing eye in sympathetic ophthalmia Whether it has any place in the treatment of an exciting eye is a question that is indicative of the difficulties that arise in the use of cortisone in almost every other condition Reduction in the inflammatory reaction of an exciting eye can reasonably be expected and is clinically obtained with the use of cortisone but this leaves the serious question whether such reduction in inflammatory reaction is masking the underlying and unknown agent which produces sympathetic ophthalmia Judging by the experimental work on tuberculous infection of the eye the masking of inflammatory reaction in such eyes renders such treatment unjustifiable in ocular tuberculosis and the same may possibly apply to cortisone treatment of the exciting eye in sympathetic ophthalmia

The favourable effect of cortisone on the eye acutely inflamed from interstitial keratitis is readily explained by the reduction of the inflammatory processes but the severe relapses that are being seen fit in with the rebound phenomena observed in



(a)

FIG 13 —Cortisone treated immune allergic rabbit (a) globe showing buphthalmos necrosis and caseation of globe 32 days after cessation of treatment (b) iris showing necrosis and caseation after cessation of treatment (*By courtesy of the British Journal of Ophthalmology*)



(b)

Clinical possibilities and limitations

The available experimental work is not sufficiently extensive to give a final answer as to the possible uses of cortisone

CLINICAL ASPECTS

Methods of administration and dosage

Local cortisone treatment is usually sufficient in lesions of the anterior segment Disease of the posterior segment may respond only to systemic therapy

Local administration

This must necessarily be by cortisone as ACTH is only active through the adrenal gland not locally

Drops —The commercial suspension of 25 milligrams of cortisone acetate per millilitre of saline solution with 1 5 per cent benzyl alcohol is slightly irritating to the eye Diluted 1 4 with normal saline solution or a buffered solution it is non irritating and clinically as effective as the stronger solution The addition of a wetting agent for example Zephiran may improve penetration Initial dosage in an acute case is 1 drop hourly When a satisfactory response is obtained the dosage is progressively reduced to 3 or 4 drops daily

Ointment —This has been used in strengths from 10 milli grams to 25 milligrams per gramme the usual concentration being 15 milligrams per gramme in a lanolin or other oil in water base The ointment is applied 3 hourly in acute cases and can usually be reduced to a maintenance dose of one or two applications daily

Subconjunctival injection —The dose employed is from 0 2 to 0 4 millilitres usually the latter dose of the commercial suspension The injection may cause slight conjunctival reaction and is seen as a white plaque under the conjunctiva This plaque may be present for a week or more but its persis tence does not necessarily indicate that active material remains Injections are usually given at 2–3 day intervals in an acute case but may be reduced to weekly intervals after 2 or 3 injections or maintenance dosage may be continued with drops or ointment

No appreciable systemic effect is produced by the topical use of cortisone It can therefore be used for long periods and in patients for whom systemic treatment would be contra indicated It occasionally causes a local allergic drug reaction

other clinical spheres when such essentially symptomatic treatment is suspended

Infective conditions

In infective inflammatory reactions as opposed to non infective inflammation the scope for cortisone would therefore appear to be distinctly limited until such time as a combined therapy against both the infection and the inflammatory process becomes possible Whether such combined therapy will be necessary remains an open question for in the spheres where the sulphonamides and the antibiotics are effective the control of infection carries with it the control of the inflam matory reaction

Other affections

Clinically many of the chronic inflammatory diseases are of unknown origin It would appear that such cases as are infective in origin are hardly suitable for cortisone treatment As for the chronic inflammatory cases of non infective origin until adequate means are available to treat the unknown underlying state cortisone has at best a place only as an emergency measure to control an excessive inflammatory reaction In repair of wounds of the cornea and particularly in the care of the newly inserted corneal graft there appears to be room for the cautious use of cortisone in doses that help to diminish vascularization without actually interfering with repair That such a procedure may indeed be feasible is suggested by the experimental results with caustic injuries of the cornea

Such considerations all lead to the conclusion that in the use of cortisone the maximum tolerated dose—tolerated by the body or the eye—is not necessarily the optimum dose They pose forcibly the question whether it is possible to influence in a fractional way such a relatively complex process as inflammation and they emphasize the need for a better understanding of the aetiology of the various inflammatory reactions

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Systemic treatment with ACTH or cortisone

If systemic treatment is to be used for eye disease the same care and attention to dosage must be exercised as for general disease (*see* page 37) In general terms the patient is started on full dosage If a response is obtained the dose is then gradually reduced until a maintenance dose is found This is continued until the lesion is quiescent, or in some cases a change may be made to local therapy A course of systemic treatment may occupy from 1 to 3 weeks and sometimes a maintenance dose may have to be continued for longer to prevent recurrence

Disorders in which cortisone and ACTH are effective

The ocular conditions which have shown a good response to cortisone and ACTH are essentially acute inflammatory reactions of limited duration There is rapid improvement in the inflammatory signs and symptoms but relapse is common unless the underlying cause of the reaction has been successfully treated by other methods or has ceased to be active Relapse may respond satisfactorily to therapy

Local therapy

Early interstitial keratitis of syphilitic origin and acute exudative iritis and iridocyclitis are conditions in which there is a good response to local therapy

Early interstitial keratitis —Most cases show rapid improvement Treatment may have to be continued as a maintenance dose for long periods to prevent relapse Local treatment gives better results than systemic administration and ointment or drops seem the method of choice Energetic anti syphilitic treatment should be carried out concurrently with hormone therapy In late cases old corneal scarring is not improved by cortisone though any active inflammation may respond In the stage of corneal necrosis it is possible that therapy may do harm by inhibiting the normal process of repair It is not yet possible to assess the long term results of apparently successful early treatment

Acute exudative iritis and iridocyclitis —A rapid response to topical therapy may be expected in a high proportion of cases The better aqueous concentration produced makes subconjunctival injection the route of choice at least for the initial treatment If early improvement reveals that a severe exudative reaction has masked an underlying focal or nodular process cortisone therapy should only be continued with great caution as it may inhibit tissue reactions to localize the infection Post operative and traumatic iritis often respond well in the early acute stage

Conditions showing symptomatic relief—These include spring catarrh allergic conjunctivitis and episcleritis

Conditions showing symptomatic relief and resolution of early corneal infiltrates —These conditions include active phlyctenular keratitis rosacea keratitis early sclerosing keratitis and some ill defined acute corneal reactions with active infiltrations or vascularization

Combined local and systemic therapy

Sympathetic ophthalmia —It is too early to assess the part cortisone will play in the prevention and treatment of this disease It is not yet certain whether the control of inflammation in the damaged eye by cortisone will protect its fellow or merely suppress the recognized danger signals In the established disease inflammatory signs and symptoms may respond well in both the exciting and sympathizing eye particularly in early cases If local treatment fails systemic treatment including if necessary intravenous ACTH is sometimes successful Relapse after treatment is common and naturally therapy does not affect established changes such as cyclitic membrane synechiae or cataract It may however make it safer to operate when necessary as therapy can be used to minimize post operative inflammation

Systemic therapy

Acute exudative choroiditis —A good response is often obtained to systemic therapy If there is reason to suspect that the choroidal lesion is due to an infection for example with

the tubercle bacillus, hormones if used, should be given very cautiously and should be accompanied by suitable chemo therapy

Diseases in which cortisone is ineffective

Degenerative disease and established cicatricial lesions have shown no response to cortisone neither have exudative lesions in which the exudation was not inflammatory in origin Hormone therapy has also been tried for various diseases of unknown aetiology without success

The more significant of these conditions are shown in the Table on page 97

Individual cases may show some palliative effect upon secondary inflammatory symptoms but the underlying condi tion remains unchanged

Disorders which show a variable or partial response to cortisone

There remains a large group of disorders in which cortisone and ACTH have been used with very variable results Some of these disorders are chronic inflammations which may show a partial response but which may relapse rapidly on the cessation of treatment In some the results are hard to assess because of the tendency of the disease to undergo spontaneous remission

The more significant of these affections fall into the following categories

Inflammatory reactions —Drug irritation scleritis

Affections with exudative reactions of unknown aetiology — Some cases of secondary glaucoma hypertensive uveitis chronic uveitis

Presumed virus diseases —Some cases of superficial punctate keratitis dendritic ulcer disciform keratitis herpes zoster keratitis and uveitis Behcet s syndrome

Affections of ill understood origin —Retrobulbar and optic neuritis malignant exophthalmos uveal sarcoidosis opaci fication of a corneal graft and central serous retinopathy

TABLE

SOME OF THE MORE SIGNIFICANT AFFECTIONS THAT HAVE SHOWN NO RESPONSE TO CORTISONE THERAPY

	Inflammations	*Vascular degenerations*	*Exudative reactions of unknown origin*	*Genetic affections*	*Affections of unknown origin*	*Ill defined entities*
Cornea	Mustard gas keratitis			The corneal dystrophies	Band shaped opacity Mooren s ulcer	Nebulae
Lens					Cataract	
Vitreous					Eales disease	
Retina and choroid		Diabetic retinopathy arterio sclerotic retinopathy venous thrombosis	Senile exudative reactions at macula Coats disease	Retinitis pigmentosa and allied conditions		
Optic nerve						Optic atrophy
Globe as a whole					Retrolental fibroplasia primary glaucoma	
General ocular disease					Sjögren s syndrome	

Most of these affections present difficulties in clinical differentiation as to the underlying pathology It is perhaps for this reason that reported results are inconstant and conflicting

Contra indications

These like the indications for treatment are as yet not clear The caution needed in the use of cortisone in sympathetic ophthalmia and in interstitial keratitis have already been indicated as have the possible serious sequelae in ocular tuberculosis It is likely that the use of cortisone in all uncontrolled infections of the eye is fraught with danger

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CHAPTER 3

ENDOCRINE DISORDERS

CORTISONE is a steroid of the adrenal cortex whatever its future place in the therapy of disorders of other systems it seems obvious that its place in the treatment of endocrine disorders is more logical and less empirical than elsewhere and more likely to survive as orthodox therapy

Generally speaking in the treatment of endocrine disorders gland replacement therapy is more effective than stimulation therapy the treatment of myxoedema with thyroid extract or sodium laevo thyroxin is for example one of the most satisfactory things in medical therapeutics all the signs and symptoms of the disease gradually disappearing with complete restoration to normality of a patient who was previously extremely ill Cortisone in several endocrine disorders is already orthodox effective therapy and there is less argument as to its correct use in this field than in any other field of therapeutics Hydrocortisone (compound F) has been shown in the main to have similar actions variations in intensity of action being due to differences of absorption by different routes rather than essential changes in its effect on metabolism In Great Britain however it has hardly been used at all in endocrinological disorders Discussion is therefore largely confined to cortisone (Kendall s compound E)

ADDISON S DISEASE

Addison s disease is the result of adrenal cortical destruction It is the result of withdrawal of those hormones produced in the adrenal cortex Replacement therapy by such hormones is entirely logical and very effective

The adrenal cortex is unlike the medulla essential for life Its destruction results in upset of electrolyte balance carbo hydrate metabolism renal function and resistance to infections and other forms of stress The sequence of events in adrenal ectomized experimental animals and patients with Addison s disease is the same Sodium and chloride ions are lost in the urine The sodium ion is concerned with water balance and therefore water loss also occurs approximately 6 5 milli litres to each milli equivalent It has been estimated that the probable daily loss is in the region of 50–100 milli equivalents sodium and 300–650 millilitres water The body fluids are extracellular and intracellular Extracellular fluids approxi mately 20 per cent of body weight are a blood dialysate essentially protein free The major ionic base is sodium which determines the osmotic pressure Intracellular fluid about 50 per cent of body weight has the potassium ion as its major base Plasma volume is kept constant at the expense primarily of *interstitial (extracellular) fluids though the intracellular* component is affected when the interstitial is materially decreased In adrenal cortical insufficiency sodium and *chloride loss results in water loss primarily from extra* cellular fluid The resulting drop in osmotic pressure causes fluid migration into the cell and further extracellular *dehydration Blood volume diminishes and haemoconcen* tration occurs Diarrhoea and vomiting aggravate the picture and the patient or experimental animal passes into the stage of *shock or addisonian crisis*

In the course of the development of this state potassium the intracellular ion diminishes in the urine as its level rises in the serum the opposite of what is occurring with the sodium ion the level of which drops in the serum as it is lost from the body In the phase of recovery the reverse process sets in In Addison s disease or after adrenocortical ablation the body cannot retain its sodium Excess sodium in the diet will therefore slow the progression to crisis withdrawal will hasten it

Adrenalectomized animals given food and sodium maintain a fairly normal blood sugar and normal glycogen stores in

muscles and liver Starvation rapidly causes a drop in both Hypoglycaemic episodes occur in Addison s disease and the low blood sugar level contributes to the clinical picture

So much for the electrolytic and other changes in adrenal insufficiency What are the effects of the different effective therapeutic agents on these changes ?

Deoxycortone (DOCA) —This synthetic steroid has potent salt and water retaining capacities but in the dosage usually employed there is no effect on intermediary carbohydrate fat and protein metabolism In excess it produces oedema hypertension and potassium loss in the urine with lowered serum potassium causing muscle weakness or flaccid paralysis Cardiac failure may be precipitated Given orally four fifths is destroyed in the body and rendered ineffective though potency is preserved to a greater degree in suitable sublingual preparations

Cortisone (compound E) —This natural steroid has only one fiftieth the salt retaining potency of deoxycortone While sodium is retained potassium loss occurs early in therapy Cortisone preserves carbohydrate stores by decreasing carbo hydrate utilization and increasing that of fat Glucose tolerance is diminished On large doses such as 100 milli grams daily cortisone may lead to a negative nitrogen balance in practice however this is usually offset by the increased appetite and greater protein intake on therapy Unlike deoxycortone it is highly and rapidly effective when given by mouth

The clinical picture of Addison s disease varies greatly in severity and many mild cases early in the course of the disease are missed The cardinal signs weight loss pigmentation asthenia and hypotension may come on insidiously and separately Although non pigmented cases occur they are rare but systolic blood pressures above 100 millimetres of mercury are by no means uncommon Anorexia leading to nausea vomiting and diarrhoea or constipation often with severe abdominal pain are symptoms of crisis and call for rapid and effective action Such a crisis may be and often is

precipitated by a surgical operation or an acute infection Pigmentation may apparently deepen in such crisis due to dehydration and cyanosis

Diagnosis of Addison's disease

The fully developed picture of Addison s disease can hardly be missed but mild or early cases may present real difficulties in diagnosis A number of diagnostic tests have therefore been evolved depending on aggravation of the condition by salt restriction and administration of potassium (Cutler Power Wilder test) the inability of addisonian patients to show a normal water diuresis (Robinson Power Kepler test) absence of the usual drop in circulating eosinophils after injection of corticotropin (Thorn s test) and others There is as yet no test which measures directly the circulating hormone in the blood all the above tests are therefore indirect and subject to some error In the presence of an intact adrenal cortex its stimulation by corticotropin (ACTH) causes a drop of over 50 per cent in circulating eosinophils this test (Thorn s test) is negative in Addison s disease

Thorn s test together with the Robinson Power Kepler test mentioned above is the usual one performed in diagnosis the salt depletion test of Cutler Power Wilder carrying the danger of serious exacerbation of the condition is much less popular in Great Britain The subcutaneous adrenaline test of Thorn should also be mentioned In this test a subcutaneous injection of adrenaline causes anterior pituitary stimulation with in turn adrenal cortical stimulation in the normal subject with resultant drop in circulatory eosinophils This test therefore unlike Thorn s corticotropin test measures both adrenal cortical and anterior pituitary competence and is negative or much diminished in Addison s disease In Great Britain this test has generally been found to be unreliable It is clear that in Addison s disease there is no place for adrenal stimulation but every place for replacement therapy

Treatment

Before the advent of cortisone Addison s disease was treated according to the severity as follows

Grade I—These mild cases were maintained satisfactorily on salt alone up to 30 grammes daily being given in capsules Potassium was frequently restricted in the diet In the face of infection or stress of any sort such a case could pass into higher grades and need additional (hormone) therapy

Grade II—More severe cases in addition to salt needed hormone (deoxycortone) therapy at frequent intervals

Grade III—These needed continuous hormone therapy

Grade IV—Grade IV cases in crisis or in pre crisis states needed cortical extract intravenously in glucose saline infusion probably with intramuscular deoxycortone in addition antibacterial agents to counteract infection and general measures to counteract shock

In maintenance therapy deoxycortone acetate was given daily by intramuscular injection until the minimal dose was discovered which would maintain weight blood pressure and general well being during an observation period of several weeks The occurrence of oedema or hypertension would lead to reduction of the dose When the minimal adequate dosage was discovered in most cases pellet implantation was given dosage being about 125 milligrams in pellet implant for every 1 0 milligram of deoxycortone previously needed by daily injection Such implants were given under sterile operating room conditions each pellet being implanted into a separate deep subcutaneous pocket Such implants would last for a period of 9 months Crystalline implants given by intramuscular injection every 2–3 weeks were an alternative form of therapy

Such therapy though effective for some years in most cases held certain disadvantages Deoxycortone is a drug which can cause serious symptoms of overdosage with salt retention oedema and hypertension and in cases with early cardiac decompensation complete failure could be precipitated

Daily injections were unpleasant for the patient and implants were sometimes extruded sometimes became infected and sometimes caused symptoms of overdosage Putting in several months dosage at one time is remote control therapy and inelastic in the face of changing needs

Cortisone has been used both by intramuscular injection by implant and by oral route in the treatment of Addison s disease with great success In the author s experience the well being and increase in energy is in excess of that seen on any previous therapy The advantages of oral therapy are obvious and it is interesting that the dosage required 12 5–37 5 milligrams a day is so small compared with that required in treatment of other non endocrinological conditions after total adrenalectomy a patient may satisfactorily be maintained on this dosage

On this basis it is now possible to re state the therapy for this condition in its different grades of severity

Grade I—These mild cases can be maintained on salt alone given in enteric coated capsules up to 30 grammes a day In face of stress of any sort if symptoms reappear cortisone may be given orally in doses of 12 5 milligrams twice or thrice daily as required discontinuing when the condition is again controlled

Grade II—More severe cases need regular routine dosage of 12 5 milligrams of cortisone 1–4 times daily by mouth or 25–50 milligrams by intramuscular injection daily Salt may be given as found necessary—a supplement of 4–6 grammes a day is usual

Grade III—In certain cases response may not be entirely satisfactory and the electrolyte balance only imperfectly restored In such cases 1–3 milligrams of deoxycortone may be given daily in addition though usually only 1 milligram is necessary Implants may be given in such cases if regular dosage of deoxycortone is required 100–125 milligrams being given for each 0 5 milligram required daily intramuscularly Many clinicians still prefer because of the relatively weak mineralocorticoid action of cortisone

to balance the patient on deoxycortone and only later to add such doses of cortisone as are necessary for production of full therapeutic effect usually 12 5–25 milligrams Cases do occur where the strong mineralocorticoid action of deoxycortone is required

Grade IV—In addisonian crisis and in instances of inter current infection or surgical procedures in patients with Addison s disease at least 100–200 milligrams of cortisone should be given daily until the additional stress has ceased and normal food and fluid intake has been restored As nausea and vomiting is probably present cortisone is often best given by intramuscular injection but cortisone should be given orally if it can be tolerated in this way in doses of 50 milligrams 6–8 hourly after a loading dose of 75–100 milligrams as absorption and therapeutic effect is quicker by this route Intravenous glucose saline solution with or without cortical extract should be given if the crisis is severe and the patient collapsed In such cases absorption of cortisone from the site of intramuscular injection may be delayed at a time when quick results are most needed and vomiting may put oral therapy out of count The usual dose of adrenal cortical extract in such cases is 20 milli litres intravenously directly with 20 millilitres given by slow intravenous infusion though some workers give doses up to six times as great

Current opinion in the United States of America is that glucose should not be given intravenously in addisonian crisis without concurrent plasma or albumin administration as in the presence of adrenal cortical insufficiency it may lead to hyperpyrexia The addition of 2 grammes of dibasic potassium phosphate to a litre of 10 per cent glucose solution is said to prevent these febrile episodes Con centrated human albumin or 250 millilitres of human plasma is advocated intravenously before administration of glucose saline solution

Antibiotics are given as required in cases where infection is present even where no obvious infection exists prophy

lactic penicillin is justifiable 300 000 units of crystalline penicillin being given every 12 hours by intramuscular injection Intravenous fluids should not exceed 3 litres in 24 hours and should be discontinued as soon as fluids are tolerated by mouth As in diabetes, early treatment in pre coma or pre crisis is much more efficacious than treat ment in full coma or crisis the more time that has passed and the more advanced the condition when treatment is started the worse the prognosis Oral or intramuscular cortisone in the above dosage given early will happily abort most early crises and many more advanced ones Cortisone in such dosage over such periods will have no adverse effects unlike deoxycortone if dosage is above the thera peutic requirements hypertension will not occur and pre cipitation of cardiac failure is most unlikely Intravenous cortisone therapy has been used in certain clinics in the United States of America but the author has no experience of treatment by this route or of intravenous hydrocortisone (compound F) which given by this method in dosage of 1 milligram per hour has been reported to have completely reversed severe adrenal insufficiency within 24 hours

Cortisone has therefore altered orthodox therapy of Addison s disease and is a regular part of treatment in all grades of severity except the mildest Therapeutic results are now much better than before its advent Patients who change to cortisone from deoxycortone alone or take both substances almost invariably feel better have more energy and more strength far fewer hypoglycaemic episodes and stand up to all forms of stress far better than previously Their gain in appetite and body weight is often dramatic and is not due to fluid retention as it frequently is on deoxycortone therapy but to true increase in body tissue Gains in weight of 1–2 stones in a year are not uncommon Except in crisis more than 37 5 milligrams of cortisone daily is only very rarely required a dosage almost incapable of causing any undesirable side effects Periods of fasting are tolerated better than pre viously the blood sugar levels being maintained surprisingly

well Abnormalities of water secretion as shown in diagnostic tests such as the Kepler Power are said to be reversed if 40–50 milligrams of cortisone are given daily but only occasion ally on lower doses The blood pressure is held at normal levels and hypertension does not occur even with excessive dosage as it does with deoxycortone except in rare instances Personality changes not infrequent in Addison s disease disappear and on the small dosage used mental upsets only very rarely occur The electroencephalogram in Addison s disease is characterized by a decrease in the predominant frequency and the presence of short bursts of low frequency Cortisone reverses the characteristically slow electroencephalo gram deoxycortone alone in normal therapeutic doses does not

Precipitation into crisis by acute infection is a rarity in patients maintained on cortisone who seem to withstand and shake off infection much better than cases maintained on deoxycortone alone Thorn and his colleagues (1951) though retaining deoxycortone in routine therapy of Addison s disease in many cases because of its mineralocorticoid salt retaining action state in a summary of an account of treatment of adrenal insufficiency

The advent of ACTH and cortisone has opened a new chapter in the diagnosis and treatment of adrenal cortical insufficiency In specific stimulation of the gland by ACTH we have for the first time achieved the goal of testing adreno cortical reserve No longer must accurate diagnosis await the development of advanced disease In the realm of therapy we need not be limited to the repair of the disordered electrolyte balance by means of diet and desoxycorticosterone administra tion measures which while protecting the hypoadrenal patient against dehydration and shock yet all too often leave him more or less crippled by residual metabolic defects As shown by these preliminary studies, cortisone by filling this gap in therapy has made it possible to restore the great majority of patients to an active life Thus through the development of both a specific adrenal stimulant and adequate

lactic penicillin is justifiable, 300 000 units of crystalline penicillin being given every 12 hours by intramuscular injection Intravenous fluids should not exceed 3 litres in 24 hours and should be discontinued as soon as fluids are tolerated by mouth As in diabetes early treatment in pre coma or pre crisis *is much more efficacious than treat* ment in full coma or crisis the more time that has passed and the more advanced the condition when treatment is started the worse the prognosis Oral or intramuscular cortisone in the above dosage given early will happily abort most early crises and many more advanced ones Cortisone in such dosage over such periods will have no adverse effects , unlike deoxycortone if dosage is above the thera peutic requirements hypertension will not occur and pre cipitation of cardiac failure is most unlikely Intravenous cortisone therapy has been used in certain clinics in the United States of America but the author has no experience of treatment by this route or of intravenous hydrocortisone (compound F) which given by this method in dosage of 1 milligram per hour has been reported to have completely reversed severe adrenal insufficiency within 24 hours

Cortisone has therefore altered orthodox therapy of Addison s disease and is a regular part of treatment in all grades of severity except the mildest Therapeutic results are now much better than before its advent Patients who change to cortisone from deoxycortone alone or take both substances almost invariably feel better have more energy and more strength far fewer hypoglycaemic episodes and stand up to all forms of stress far better than previously Their gain in appetite and body weight is often dramatic and is not due to fluid retention as it frequently is on deoxycortone therapy but to true increase in body tissue Gains in weight of 1–2 stones in a year are not uncommon Except in crisis more than 37 5 milligrams of cortisone daily is only very rarely required a dosage almost incapable of causing any undesirable side effects Periods of fasting are tolerated better than pre viously the blood sugar levels being maintained surprisingly

Mrs N L aged 35 years had been perfectly well until 3 months previously She had been married 10 years and had one female child aged 7 years She had carried out her house work and in addition worked in a canteen until 8 weeks pre viously Three months previously she had what she thought was gastric flu She became shivery and vomited repeatedly There was no abdominal pain and no diarrhoea The attack cleared up in 14 days

One month later a similar attack recurred but on this occasion with vomiting She had to give up work and since this time vomiting on and off at intervals continued to be a trouble She began to feel extremely weak and took frequently to her bed for although she had no pain she had absolutely no energy Bowels were normal but for one attack of diarrhoea lasting a few days Her appetite became poor it had previously been excellent She had lost weight but did not know how much and had noticed her skin had been getting gradually browner in the past 3 months Menses were $/_{35}$ as previously but she felt more weak towards the end of the period

She was seen at hospital on 29 12 52 extremely ill pigmented blood pressure 76/50 vomiting she was brought in on a stretcher She was admitted immediately as a case of Addison s disease entering crisis As she was critically ill a 5 per cent glucose saline intravenous drip was started with Eucortone (adrenal cortical extract) 10 millilitres into the drip and 10 millilitres intramuscularly Cortisone 200 milligrams was given 100 milligrams into each buttock Deoxycorticosterone (DOCA) 10 milligrams was given intramuscularly and 5 milli grams subsequently 6 hourly for 6 days Penicillin intra muscularly was given 250 000 units 6 hourly

She steadily and slowly improved and was maintained on 5 milligrams of intramuscular DOCA daily This was changed when she appeared completely stable to crystalline DOCA injections every fortnight On this she continued well as an out patient and she was considered as satisfactory from the view point of an average case of controlled Addison s disease Her blood pressure varied from 115 75 to 90/60 The last figure was in a week when she had a cold and had been rather busier at home also in this week menses had been rather heavy

It was found that one injection of crystalline DOCA lasted her just a fortnight She was then changed to cortisone On this she gained weight from 7 st 6 lbs to 8 st 4 lbs in a 4 month period She said she felt *marvellous* and *had never* felt so well The dosage was 12 5 milligrams by mouth three times daily On this her blood pressure remained around

amounts of potent synthetic adrenal steroids adrenal cortical insufficiency is no longer the obscure and deadly disease of the past, but a state to be frequently anticipated, easily recognized and successfully treated

It may be asked as Addison s disease is frequently the result of tuberculous destruction of the adrenal cortices whether there is a risk of exacerbating tuberculous disease in the body The answer is that although larger dosage is known to have this effect smaller dosage only very rarely has and may be considered safe Nevertheless all cases before therapy is started should be examined carefully clinically and radiologically for any evidence of active or quiescent tuberculous disease anywhere in the body

Diabetes co existing with any other disorder always alters the therapy of both conditions Addison s disease is no exception to this general rule (*see also* page 125) Patients suffering from both these disorders seem to be extraordinarily sensitive to small doses of cortisone—even 12 5 milligrams of the hormone causing increased insulin requirements On larger insulin dosage however control is as effective as previously though early crisis may completely upset normal diabetic balance and require very careful handling

Does pigmentation alter on cortisone therapy ? The answer to this question is in most cases no even after prolonged treatment Some cases have however been reported of definite reduction in pigmentation one within a few weeks of starting treatment but they must be considered exceptional the rule is for patients to continue to be pigmented but with muscle strength energy appetite and general health restored

In the preamble earlier in this chapter attention was drawn to the fact that Addison s disease is essentially a biochemical upset characterized by sodium and fluid loss Cortisone has much less effect than deoxycortone on salt retention it is of interest to note that in spite of this fact it is an extremely effective drug in the routine day-to-day treatment of this condition and of greater interest still it is effective in the therapy of addisonian crisis

vene in some neither signs of adrenal insufficiency nor a drop in blood pressure occur Patients with raised blood pressure after adrenalectomy may not show a low blood pressure until actual adrenal crisis occurs the blood pressure level is there fore useless as a guide to adrenal substitution therapy in such cases The place of cortisone in the treatment of Cushing s disease is described in the section on that disease

Acute adrenal destruction by haemorrhage occurs rarely in the later stages of pregnancy in haemorrhagic conditions in meningococcal septicaemia (Waterhouse Friderichsen syn drome) and other forms of severe prostrating infection The use of cortisone in the face of acute adrenal insufficiency of this nature is logical and cases have been reported where it appears to have been life saving Used in cases of meningo coccal infection no adverse effect was noted on concurrent antibiotic therapy Dosage should be large as in addisonian crisis but smaller doses such as 25 milligrams 4 times daily have been reported on as effective Working on the theory that some cases of severe post operative shock are in fact due to adrenal exhaustion corticotropin (ACTH) has been tried but though occasional patients have done well most have shown no improvement and in the author s small experience little is to be expected in such cases It has been found that there is no evidence of adrenal exhaustion in the average post operative case as judged by adrenal response to injected corticotropin

ANTERIOR PITUITARY INSUFFICIENCY (SIMMONDS S DISEASE SHEEHAN S SYNDROME)

In Addison s disease the defect lies in the loss of one essential endocrine gland in Simmonds s disease loss of the hormones secreted by the anterior pituitary leads to atrophy and under secretion of a number of other endocrine glands and the effects are far wider far more diffuse and far more variable

The commonest cause in the author s personal experience is the post partum necrosis so well described by Sheehan in Great Britain (1939 1949) The march of events is usually

120/75 and her energy and well being were in excess of her previous condition She says she feels vastly better on cortisone than she ever did on DOCA alone So far over a 9 month period there is no sign of any salt deficiency although she only takes as much as she feels she wants

Comment

This case brings out several points One is that even in the most obvious cases diagnosis may still be missed and patients with Addison s disease arrive at the clinic or surgery for the first time in pre coma or even coma The second point is the obvious improvement on changing from deoxycortone crystalline implants to cortisone In the treatment of the early crisis in this case we erred on the side of safety and gave everything we had as we feared a fatal result certainly in the light of what has been learnt since much of this therapy may have been unnecessary but some clinicians still prefer to use deoxycortone cortical extract and cortisone in crisis of this sort Finally this patient has been instructed as to the fact that she has a disease which like diabetes or myxoedema will be with her for life Maintenance therapy is therefore her the patient s concern and it is up to her to increase dosage in the face of any stress or infection and to report rapidly to the clinic or to her practitioner as in diabetes The addisonian patient must know the dosage of her drug something of her disease and the management of it and most particularly what aggravates it Timely increase of dosage in face of intercurrent infection will prevent many a crisis

Treatment of the adrenalectomized patient

In the last 2 years an increasing number of patients have had bilateral total or subtotal adrenalectomy performed for a variety of conditions—Cushing s syndrome carcinoma of the prostate schizophrenia and hypertension In such patients where total adrenalectomy has been performed substitution therapy with cortisone is at present the usual practice 12 5–50 milligrams being given daily by mouth in divided doses with salt supplements as and if required The problem is essentially the same as in Addison s disease but the adrenalectomized patient often behaves rather differently from the addisonian After adrenalectomy for hypertension for example results are variable in some the blood pressure remains elevated after operation even though signs of adrenal insufficiency super

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showed weight loss Such discrimination precluded all plump cases and nullified the aim of the review

This clinical picture is emphasized as diagnosis is on the history and clinical examination side room tests may mislead as will appear from what follows later

To produce this clinical picture of Sheehan s syndrome over 75 per cent of the gland must be destroyed it is amazing what a small particle of intact gland will maintain normal function and prevent development of the disease In some severe cases life has been precariously maintained on some 6 per cent of gland tissue

Other causes of hypopituitarism are injury basophilic adenoma of the pituitary cyst of Rathke s pouch (cranio pharyngioma) destruction by a cerebral tumour in the region of the third ventricle or any other expanding lesion in the region of the pituitary basal meningitis cavernous sinus thrombosis and malignant hypertension are very rare causes Deep x ray therapy to the region of the pituitary may preci pitate signs of anterior pituitary insufficiency After complete investigation some cases show no sign of primary lesions and fall into the inevitable class of idiopathic hypopituitarism Anorexia nervosa initially a mental disturbance eventually manifests in almost identical manner with signs and symptoms of secondary hypopituitarism the primary diagnosis here lies essentially in the history and there is no doubt that con fusion in diagnosis between primary and secondary condition has led previously to difficulties in true assessment of cases

An eosinophilic adenoma may expand to almost complete destruction of the anterior pituitary symptoms of hypopitui tarism may be then grafted onto the picture of a previous acromegaly

The anterior pituitary secretes the gonadotropic hormones (LTH or luteotropic hormone LH or luteinizing hormone and FSH or follicle stimulating hormone) It also secretes corticotropin or adrenocorticotropic hormone (ACTH) soma totropin or growth *hormone the thyrotropic hormone (TTH)* and possibly others Withdrawal of these hormones leads to

as follows a woman previously absolutely normal and at full term goes into labour Profuse haemorrhage occurs usually from a placenta praevia, manual removal of which in some cases adds uterine infection The patient is extremely ill and shocked and has become extremely anaemic very rapidly as a result of profuse blood loss Recovery is slow From the moment of haemorrhage the patient is a different woman even when her blood picture is restored to normal Lactation is impossible and the child has to be artificially fed Menses do not return The patient suffers marked lassitude and becomes wizened in face though her body does not waste and weight is usually within normal limits, she may even be plump Hair falls from axillae pubis head and face and she becomes peculiarly pale and hairless even fine body hair being diminished The pallor though perhaps partly caused by anaemia is largely an actual depigmentation even the areolae of breasts of multipara become pale and depigmented Episodes of weakness and actual coma occur and blood sugars are found to be at low levels at normal times and at low hypoglycaemic levels in coma In coma the patient is peculiarly cold and rigid to the touch she is almost cadaveric Although other factors salt depletion for example may enter the picture hypoglycaemia is the main and principal feature in most of such episodes Her mentality changes she becomes difficult sluggish and perhaps actually psychotic Mentally and physically in the space of a few weeks she has become a completely different woman from previously

Amenorrhoea continues In most cases she is then diagnosed as a case of mental disease or myxoedema the treatment of either condition producing anything but a beneficial result The true diagnosis is often missed as in the absence of wasting Simmonds s disease is frequently not considered Sheehan has frequently emphasized that wasting need not be present many of his photographs of such cases taken at autopsy show plump well nourished subjects Nevertheless when Escamilla and Lisser (1942) reviewed the world s literature of Simmonds s disease in 1942 only those reported cases were accepted who

of adrenal cortical activity by intravenous or intramuscular injections of corticotropin the test becoming negative again within a few days of discontinuing injections 17 Ketosteroid output in urine is at a low level in untreated cases rising temporarily under corticotropin stimulation The adrenal cortex can therefore be goaded into activity but only temporarily by corticotropin

Treatment

Prior to the advent of cortisone and corticotropin therapy of Simmonds s disease was unsatisfactory it still leaves something to be desired Frequent 2 hourly feeds to prevent hypoglycaemic episodes and intravenous glucose in such episodes were usual Infections were rapidly combatted by antibiotics and sulphonamides and early hospitalization Care was taken to avoid heavy stresses of any sort Thyroid administration sometimes had no effect sometimes made the patients feel worse and in full dosage occasionally precipitated a crisis of addisonian type The most useful of a not very useful selection of drugs was testosterone given by intramuscular injection as propionate or by pellet implant This caused some increase in energy libido and well being and sometimes increased hair growth Salt and water retention was promoted with testosterone the opposite effect was seen with full thyroid dosage water and salt loss occurring Various endocrine therapeutic mixtures were evolved containing thyroid testosterone and deoxycortone but therapeutic results were not impressive and testosterone alone seemed to be as effective Treatment of an underlying neoplastic lesion by surgery or irradiation sometimes worsened the features of hypopituitarism Mild cases of Sheehan s syndrome who became again pregnant—a rare event—sometimes improved greatly after the birth of the new child but cases have occurred where further fatal anterior pituitary destruction occurred at childbirth

Treatment by stimulation of the adrenal cortex was first undertaken by the author Courses of intramuscular corticotropin were given the dosage being 100 milligrams a day

involution of other glands and organs Withdrawal of gonadotropins leads in man to *hypogonadism*—the genitalia become small libido slight or absent and the subject infertile In woman menses cease, breasts usually become smaller and lactation ceases Withdrawal of thyrotropin leads to cold intolerance, a lowered basal metabolic rate diminished iodine uptake facial features sometimes resembling those of myx oedema and slowing of body functions including cerebration Serum cholesterol rises and to most routine current laboratory tests the patient appears to be suffering from myxoedema electrocardiographs being typical of this condition This secondary myxoedema resulting from hypopituitarism differs from the primary idiopathic variety in that the skin and hair is usually of finer texture the voice rarely takes on the croaking raven quality and the peculiar pallor differs from the waxy yellow pallor with malar pink flush seen in primary sub thyroidism Withdrawal of growth hormone results in visceral under development uterus ovaries kidneys heart liver and other organs being smaller than normal Withdrawal of corticotropin leads to secondary addisonian features princi*pally loss of energy and a somewhat lowered blood pressure* An essential point of difference lies in the absence of pigmentation in Simmonds s disease Islets of Langerhans secrete unopposed by anterior pituitary hormones and hypo glycaemia is the rule The clinical picture is therefore a complex one and capable of some variation

Diagnosis

Many patients are taken to be cases of myxoedema as noted above, although history and clinical examination should give the correct diagnosis *Mental derangement may cause con*fusion in diagnosis Thorn s adrenaline test is negative Using Thorn s ACTH test the first injection of corticotropin fails to produce eosinopenia though after 6 hourly injections for 48 hours the test usually converts to positivity eosinophils dropping below 50 per cent of the preceding fasting figure Similarly the water tolerance test of Robinson Power Kepler initially negative becomes positive after repeated stimulation

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6 hourly by intramuscular route gradually reducing to 40 milligrams or lower over a period of 1–3 weeks In some cases 20 milligrams were given by intravenous infusion over an 8 hour period daily for 6 consecutive days, the adrenal stimulation obtained by this route being greater than that seen on the larger intramuscular dosage Therapeutic results from these booster courses were gratifying up to a point but though general well being lasted for some weeks subsequently tests of adrenal cortical function were found to have become abnormal again within a few days of stopping therapy Week end injections of 50–100 milligrams of corticotropin intramuscularly did not maintain well being and hypoglycaemic episodes occurred though not within 3 weeks of a full course On corticotropin alone the results obtained by the author in 5 cases in a total of 8 courses of treatment could be tabulated thus (1) Increase in energy and sense of well being disappearing after 4–8 weeks (2) Loss of cold sensitivity over the same period (3) Some slight increase in growth of hair on head extremities and body (4) Increased appetite gain in weight and increase in male libido

Some of this improvement may have been psychological but undoubtedly not all of it Negative results were (1) Electrocardiographs were unchanged (2) Basal metabolic rates and radioactive iodine clearance tests were unchanged (3) Menses did not return

Hypoglycaemic episodes tended to recur 4–8 weeks after courses of therapy and sometimes heralded complete and rapid relapse to the initial state though not invariably Investigations showed (1) Thorn s corticotropin adreno cortical stimulation tests initially negative became positive after 2 or more days therapy in most cases (2) Robinson Power Kepler tests gave low (negative) readings During therapy they reverted to normal only to relapse 2 days after treatment was stopped (3) Urinary ketosteroid output usually rose slightly from a low figure and fell rapidly after cessation of therapy

Interesting case histories are the following

Mr D B aged 38 years had been concussed twice at the age of 17 and 18 years but was perfectly fit and well until 1941 when in the Army stationed on the end of Southend Pier and sleeping in a well ventilated draughty room without a fire he awoke one morning in a daze unable to stand and only semi conscious He was admitted to hospital for 14 days His symptoms reappeared on his return and he spent the next year almost entirely in hospitals and convalescent homes In 1942 he was diagnosed as a case of myxoedema and thyroid extract prescribed He continued on this treatment until March 1951 without apparent effect He gradually became a typical case of Simmonds s disease His libido disappeared he shaved only once in every 1 or 2 weeks he became lethargic and irritable Coitus was only achieved once every 2 or 3 months On admission in April 1951 he was a typical case of Simmonds s disease No evidence was found of a progressive neurological lesion A course of ACTH was given totalling 310 milligrams over a period of a week administered 6 hourly intramuscularly Thorn s test at the commencement and on the fourth day of therapy was negative On the second day of therapy he noticed more energy and was less cold than pre viously By the fourth day he had abundant energy and was spending much longer out of bed He was discharged on 21 5 51 and remained well and full of energy until 14th June shaving daily and indulging in coitus nightly He noticed an increase in the hair over arms and legs and felt much stronger On 14th June he entered a public house and before ordering a drink started to play snooker He then experienced one of his by now well known faint turns and was assisted home and given glucose Over the next fortnight he lost most of the improve ment he had made previously The period of improvement therefore was 28 days only after the last injection He was re admitted on 11 7 51 He was so anxious to receive more treatment that to note the psychological effect control injections of saline solution were given On these his energy improved he walked about more briskly and stated he began to notice the improvement on the third day of the injections On 25 7 51 20 milligrams of ACTH was given daily in 1 pint of normal saline solution by intravenous drip over a period of 8 hours This was repeated on 5 days subsequently a total of 120 milligrams of ACTH by intravenous administration over a period of 6 days Thorn s test negative at the onset of the course and on his previous admission on the day following the end of the course was positive Energy returned in excess of that noted with the

control injections and he was discharged on 15 8 51 Subsequently week end injections of 40 milligrams of ACTH intramuscularly were given but these did not maintain him in good general health and he had little energy ACTH injections were then given twice weekly but with little improvement In March 1952 testosterone injections were recommenced the long acting crystalline preparations being used On this he improved 1 injection being given every 3 weeks and on this he was better than he had been on twice weekly ACTH One hypoglycaemic episode occurred nevertheless in May and as usually happened his condition deteriorated rapidly subsequently Treatment was then changed to cortisone 12 5 milligrams twice daily by mouth This was increased on 1st July to 3 times daily On this dosage his general condition improved he states he is perspiring more than previously and his libido has vastly improved On cortisone he continues to be in good general health and quite as well as on completion of a course of ACTH He prefers cortisone to any previous form of therapy and states he feels better on it

Comment —It was clear that the use of corticotropin was unsatisfactory in that injection therapy could not be kept on indefinitely and relapse would occur if discontinued After in patient courses of therapy week end booster injections were not enough to maintain well being Adrenal cortical stimulation was therefore abandoned and cortisone was substituted Satisfactory results have since been maintained on oral therapy dosage being 25-37½ milligrams of cortisone daily in divided dosage On this no further hypoglycaemic episodes have occurred

Mrs E K aged 38 years was admitted as an emergency case in hypoglycaemic coma on 30 3 51 She proved to be a case of Simmonds s disease of only 10 months duration following the birth of her second child Her history was typical of Sheehan s syndrome but in addition there was a history of sub total thyroidectomy for thyrotoxicosis in 1936 Blood sugar was 58 milligrams per cent on admission She was given 30 millilitres of 25 per cent glucose solution intravenously She rapidly improved and asked where she was complaining bitterly of the cold It was decided to try the effect of ACTH immediately to see if there was any effect on the clinical picture at this stage An intramuscular injection of 50 milligrams was given *statim* The patient 4 hours later was in deep hypoglycaemic coma and 20 millilitres of 50 per cent dextrose solution was given again with dramatic effect ACTH was continued 25 milligrams

6 hourly for 13 days then reduced to 10 milligrams 6-hourly for 1 day the fourteenth day of therapy Total dosage given was 845 milligrams After the seventh day of treatment she experienced much improved energy and no longer felt the cold acutely On leaving hospital on 27 4 51 she was 9 pounds above admission weight Seen 1 month later she stated she felt well—the best she had felt for years—full of energy but she still felt the cold She talked more quickly and was more full in the face Her weight was the same as it was on discharge from hospital On 15 6 51 2 months after her last injection of ACTH she was admitted to another hospital in hypoglycaemic coma her blood sugar being less than 25 milligrams per cent Intravenous glucose 60 millilitres of a 50 per cent solution was followed by oral glucose and she made a good recovery In spite of warning advice thyroid extract 1 grain daily followed by 2 grains daily was given over a period of a week—a total of 10 grains by mouth This led to a severe febrile episode with vomiting closely resembling an addisonian crisis from which she was resuscitated by stopping the causative drug and giving glucose saline solution intravenously Testosterone propionate given every other day led to no improvement She was trans ferred to our care on 14 8 51 the picture being as she was a few days after her initial admission Thorn s test was negative ACTH was started 15 milligrams four times daily reduced to 10 milligrams four times daily Improvement was noticeable on the third day After the course had been completed a single injection of 25 milligrams of ACTH for Thorn s test produced a reaction consisting of sweating constriction in the chest and the feeling of a lump in the throat The cause of this reaction remained unknown it was treated as though it were an allergic state The Robinson Power Kepler test became normal while on therapy but relapsed a few days after the last injection She subsequently remained well and felt much more energetic for a fortnight when hypoglycaemic episodes recurred four times in all within a month of discharge from hospital Cortisone was therefore started in October 1951 being given in a dosage of 12 5 milligrams twice daily On this she com menced to gain weight and felt much better Hypoglycaemic episodes have not recurred since she has been on cortisone now a period of 16 months In December 1951 sodium 1 thyroxine 0 1 milligram daily was given in addition to cortisone In January 1952 in the fifth month of cortisone therapy menses returned and have been recurring since monthly though very scanty Thyroxine was subsequently increased to 0 2 milligram a day and in the last 2 months cortisone has

been raised to 50 milligrams a day in divided dosage Her serum cholesterol has now returned to a normal figure for the first time she has gained 5 pounds in weight in the last year and looks and feels quite a different person

Comment—This case of Simmonds s disease (Sheehan s syndrome) was of much shorter duration than the others Menses failed to return on testosterone and ACTH therapy but returned on giving cortisone Hypoglycaemic episodes appear to have been completely abolished by cortisone and her improvement is in excess of that seen on any previous form of therapy

It is apparent that much can be achieved by restoring the missing adrenocortical component only in this disease but on cortisone alone thyroid function remains low and basal metabolic rates and electrocardiographs abnormal Most workers are therefore now giving additional hormone preparations—thyroid or sodium 1 thyroxine being the usual first addition Androgens and oestrogens mav also be included and sometimes salt and deoxycortone also The mental state remains satisfactory or improves but in occasional cases acute mental upsets have been reported Miliary tuberculosis has also been reported on cortisone therapy in this condition To date however substitution therapy using oral cortisone is the treatment of choice in this condition with thyroid given orally in addition and possibly other hormones as noted above On this regime well being appetite and weight are as good as on corticotropin and are better and more easily maintained Libido returned in the male case reported above on cortisone as it did on corticotropin Episodes of hypoglycaemic coma have so far not been seen in the author s series since cortisone therapy was started However results in therapy are still imperfect—a patient with Simmonds s disease remains a Simmonds s disease though improved in most cases

One further use of cortisone should be mentioned in this connexion Patients undergoing operation on tumours in the region of the hypophysis may be put onto cortisone immediately after operation or even 2 days beforehand the dosage being raised or withdrawn as found necessary Caughey James and Macleod (1952) drew attention to the post operative

mortality in cases of pituitary tumours and the fact that some writers suggest that one of the chief causes of death in such cases may be an endocrine failure They record details of 4 patients with pituitary tumours with varying degrees of hypopituitarism In 2 cases cortisone was given for post operative coma In the first case operation was on a chromophobe adenoma of the pituitary gland with bitemporal hemianopia and hypopituitarism After surgical removal of the tumour the patient failed to rouse completely and 36 hours later was confused disorientated and incontinent He became increasingly drowsy in the subsequent 3 days Cortisone therapy was then started 100 milligrams intramuscularly *statim* with 50 milligrams 6 hourly subsequently together with 0 5 millilitre of neosynephrine 2 hourly After 48 hours of this treatment there was a noticeable improvement in his condition this improvement was maintained The second case was a patient with acromegaly with a chromophobe adenoma He regained consciousness half an hour after operation but the following day became drowsy and difficult to rouse As this drowsiness increased the wound was explored nothing causative was found no improvement occurred in his condition Cortisone was started 50 milligrams 6 hourly intramuscularly but after 24 hours as his condition was worse 100 milligrams were given intramuscularly Two hours later he roused and thereafter made steady progress Where operation lies in removal or destruction of the pituitary such substitution therapy seems entirely reasonable and some workers prefer to start cortisone injections 2 days before operation decreasing the dose gradually post operatively a careful watch being kept for signs of inadequate pituitary function Finally hypophysectomy has now been performed several times in the United States of America for malignant conditions of the adrenal gland where it was hoped that removal of the adrenocorticotropic hormone would slow up the disease process Such cases have been maintained on small doses of cortisone in some of these cases however adrenal secondary deposits may have been producing adrenal hormone

CUSHING S SYNDROME

The present concept of this disease is that over function of adrenal cortices causes an over production of adrenocortical steroids and that this causes the signs and symptoms of this condition In such cases the adrenal cortex may be hyper *plastic on both sides or an adenoma or adenomas may be* present A malignant process may sometimes be found

TABLE

APPROXIMATE FREQUENCY OF SIGNS AND SYMPTOMS PER CENT IN CUSHING S SYNDROME (ADRENAL HYPERCORTICISM) (AFTER LEVINE AND WEISBERG 1950)

	Male	*Female*
Hypertension	92	92
Moon florid face	83	89
Torso obesity	*83*	*80*
Osteoporosis of bones of torso with or without fractures	64	75
Stria	75	72
Facial hirsuties	—	80
Amenorrhoea	—	64
Generalized muscle weakness	*33*	*48*
Acne	9	48
Personality changes	33	24
Testicular atrophy	17	—
Buffalo hump	42	36
Headaches	42	36
Renal calculi	17	—
Diabetes mellitus	33	26
Skin bruising	9	36
Polycythaemia	50	50

The basophil adenoma of the anterior pituitary gland described by Cushing as the causative lesion is seen occasionally—rarely an arrhenoblastoma or malignant thymoma Irrespective of the site of the lesion (ovary adrenal thymus) certain changes described by Crooke (1935) are seen in the anterior pituitary namely cytoplasmic hyalinization of the basophil cells dis appearance of the basophil granules excessive vacuolization, ballooning of the nuclei and general enlargement of the cells It seems that as in thyrotoxicosis the thyroid is the functional causative organ by virtue of over production of thyroid hormone even though a pituitary factor may be operating so

in Cushing s syndrome the disease is essentially an over production of adrenal cortical hormone whatever place the pituitary may have in different cases The resulting clinical picture is well known—plethora moon face polycythaemia obese torso head and neck with normal extremities osteo porosis sometimes with bony fractures again essentially of bones of the torso hypertension striae of skin over shoulders buttocks thighs and abdomen

The picture is therefore very similar to that seen in cortisone over dosage with certain points of difference peptic ulcera tion perforation and intestinal haemorrhage for instance reported on cortisone therapy are not seen in Cushing s syndrome

The treatment logically indicated bilateral adrenalectomy was unsatisfactory prior to the advent of cortisone Some patients died shortly after operation some survived in poor general health with low blood pressure no energy and lowered resistance to infection for longer or shorter periods cases of iatrogenic Addison s disease in fact The operation though performed was far from being satisfactory treatment Now that cortisone may cover the period of operation the outlook is entirely different Two courses are open to the surgeon to remove both adrenals *in toto* or to leave a small amount (about 10 per cent) of one adrenal cortex In both cases cortisone will be needed to cover the operation and post operative period but after total extirpation substitution therapy will be for life The operation of bilateral adrenal ectomy under cortisone cover though still a serious one is no longer the nightmare that it was previously

Walters (1952) of the Mayo Clinic described the surgical treatment of former cases Aqueous adrenal cortical extract 40 millilitres was given intramuscularly the evening before and again immediately before the operation The same extract 25–50 millilitres was given in 1 litre of saline solution during the operation Intramuscular and intravenous injec tions of the cortical extract were continued for several days subsequently After resection of the second gland most of the

patients did well for 10–20 days and then developed a delayed reaction characterized by anorexia increasing nausea and finally vomiting In some patients there were muscular and articular symptoms resembling fibrositis and periarthritis The administration of large amounts of aqueous adrenal cortical extract together with normal saline solution did not relieve this condition which in some cases persisted for 4–6 weeks Latterly cortisone has successfully replaced aqueous adrenal cortical extract both in pre operative and post operative care Walters now advises 200 milligrams intra muscularly 48 24 and 1 hour before operation Since the institution of this programme the immediate post operative shock like reaction had been largely averted and administra tion for a subsequent 48–72 hours relieved the delayed reaction If nausea anorexia fever tachycardia or vomiting appeared relief could be obtained by further cortisone administration The delayed reaction some weeks after operation characterized by weight loss anorexia lassitude and weakness could be similarly combatted It was thought by the Mayo Clinic workers (Priestly and his colleagues 1951) that prolonged or excessive administration of cortisone after operation might be unwise because it might make difficult the evaluation of the viability and functional capacity of the portion of the adrenal left behind The author however has seen sudden death with adrenal cortical haemorrhage some 10 days after unilateral adrenalectomy for Cushing s syndrome associated with uni lateral adrenocortical adenoma at a time when post operative cortisone had just been discontinued He feels that a gradually reduced maintenance dose of cortisone is indicated for some 4 weeks after operation and continues oral dosage 6 hourly as soon as the patient can tolerate it by mouth after operation dosage being dropped from 200 milligrams intramuscularly on the day after operation to 12 5 milligrams twice daily orally 1 month later Should symptoms of adrenal insufficiency appear after this time maintenance dosage has to be started at the lowest effective level Additional salt may be given as in Addison s disease In 19 cases of Cushing s syndrome

reported by the Mayo Clinic workers in 1951 3 had recurrence of symptoms of Cushing s syndrome 3 years 2 years and 9 months respectively after operation Three patients had chronic adrenocortical insufficiency and needed permanent daily replacement therapy

Huggins and Bergenstal (1951) consider the most important element in the management of patients undergoing adrenal surgery the anticipation prevention and control of post operative adrenocortical insufficiency For complete sub stitution therapy after total bilateral adrenalectomy they recommend the following scheme

Day	*Cortisone (milligrams intramuscularly)*	*Deoxycortone (milli grams intramuscularly)*
Day before operation	50 6 hourly	5 at 6 a m
Day of operation	150 1 hour before operation 50 every 4 hours post operatively	5 1 hour before operation
First post operative day	50 6 hourly	5 in 1 injection
Second post operative day	50 12 hourly	0 3 as needed

Subsequently the dosage is gradually reduced until the sustain ing dose of cortisone—25–50 milligrams daily—is reached some 7 days after operation Deoxycortone is not recom mended for maintenance therapy but salt is given in addition to cortisone 2–4 grammes daily by mouth

The following case shows in 1 patient the difference made to post operative care by use of cortisone

Mr C B aged 38 years was admitted to hospital in February 1950 under the care of Sir Stanford Cade Previously entirely normal (Fig 14) he had complained of headaches backache and loss of libido for a year On examination he was a typical case of Cushing s syndrome (Fig 15) blood pressure was 180 135 x ray examination of chest showed fractured ribs of which he was ignorant His retinae showed only early spastic hypertensive retinopathy It was decided to explore the adrenals and this was done on 16 3 50 The left suprarenal was enlarged and was removed *in toto* except for a small fragment of tissue (Fig 16) In spite of DOCA and Eucortone cover he became extremely ill and had an extremely stormy convalescence complicated by thromboses in the legs and pulmonary emboli His wound became septic further thrombosis and embolism occurred The histology of the adrenal

patients did well for 10–20 days and then developed a delayed reaction characterized by anorexia increasing nausea and finally vomiting In some patients there were muscular and articular symptoms resembling fibrositis and periarthritis The administration of large amounts of aqueous adrenal cortical extract together with normal saline solution did not relieve this condition which in some cases persisted for 4–6 weeks Latterly cortisone has successfully replaced aqueous adrenal cortical extract both in pre operative and post operative care Walters now advises 200 milligrams intra muscularly 48 24 and 1 hour before operation Since the institution of this programme the immediate post operative shock like reaction had been largely averted and administra tion for a subsequent 48–72 hours relieved the delayed reaction If nausea anorexia fever tachycardia or vomiting appeared relief could be obtained by further cortisone administration The delayed reaction some weeks after operation characterized by weight loss anorexia lassitude and weakness could be similarly combatted It was thought by the Mayo Clinic workers (Priestly and his colleagues 1951) that prolonged or excessive administration of cortisone after operation might be unwise because it might make difficult the evaluation of the viability and functional capacity of the portion of the adrenal left behind The author however has seen sudden death with adrenal cortical haemorrhage some 10 days after unilateral adrenalectomy for Cushing s syndrome associated with uni lateral adrenocortical adenoma at a time when post operative cortisone had just been discontinued He feels that a gradually reduced maintenance dose of cortisone is indicated for some 4 weeks after operation and continues oral dosage 6 hourly as soon as the patient can tolerate it by mouth after operation dosage being dropped from 200 milligrams intramuscularly on the day after operation to 12 5 milligrams twice daily orally 1 month later Should symptoms of adrenal insufficiency appear after this time maintenance dosage has to be started at the lowest effective level Additional salt may be given as in Addison s disease In 19 cases of Cushing s syndrome



FIG 16—Case C B Enlarged left adrenal removed at operation

over the subsequent 5 weeks to 25 milligrams a day by mouth He was not upset by the operation at all and he passed through the whole procedure completely uneventfully Towards the end of the month he experienced fullness of the head and other vague symptoms which were found to be due to insufficient salt intake When this was adjusted to 5 8 grammes total salt in the day these symptoms disappeared On withdrawing cortisone he rapidly became feeble felt ill and lacking in energy but as soon as cortisone was re started his symptoms disappeared It is obvious that he has no functioning adrenal cortical tissue left and that he will have to be maintained on cortisone for life At present he is on 12 5 milligrams three times daily and on this scheme he remains perfectly fit His blood pressure since the second adrenalectomy has remained normal—120 80 He has instructions to increase this dose in the face of infections or other forms of stress Histological features of the second adrenal removed which weighed 10 grammes were as follows The cortical cells are enlarged and show a particularly granular appearance Many cells show a positive reaction with Ponceau 2R There is also a profuse infiltration of round cells scattered among the other cells (George Lumb)

Comment—The most striking thing in this case was the difference at operation between adrenalectomy under cortisone cover



Fig 14 —Case C B Photograph taken prior to the development of Cushing s syndrome (1945/46)

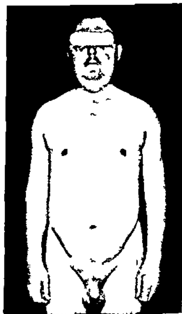


Fig 15 —Case C B Clinical appearance after development of Cushing s syndrome (February 1950)

gland removed was within normal limits though the gland as a whole was enlarged and hyperplastic weighing 5 grammes After operation he failed to improve and headaches were as severe as before He continued to gain weight and his sight became poorer He was re admitted in April 1951 when his blood pressure was 210 150 As his hypertensive retinopathy had progressed a bilateral Smithwick s operation was performed by Mr Frank d Abreu Headaches immediately improved and his blood pressure dropped to normal Further improvement was short lived and by the end of the year all symptoms had returned The blood pressure varied between 200 130 and 160 105 Dyspnoea on exertion breathlessness and attacks of vertigo had appeared Deep x ray therapy was given to the pituitary but again with only transient improvement By now cortisone was available and it was decided to remove the second adrenal under the cover of this drug Intramuscular injections of 200 milligrams were given 48 hours 24 hours and 1 hour before operation The dose was subsequently gradually reduced



FIG 16 —Case C B Enlarged left adrenal removed at operation

over the subsequent 5 weeks to 25 milligrams a day by mouth He was not upset by the operation at all and he passed through the whole procedure completely uneventfully Towards the end of the month he experienced fullness of the head and other vague symptoms which were found to be due to insufficient salt intake When this was adjusted to 5-8 grammes total salt in the day these symptoms disappeared On withdrawing cortisone he rapidly became feeble felt ill and lacking in energy but as soon as cortisone was re started his symptoms disappeared It is obvious that he has no functioning adrenal cortical tissue left and that he will have to be maintained on cortisone for life At present he is on 12 5 milligrams three times daily and on this sch me he remains perfectly fit His blood pressure since the second adrenalectomy has remained normal—120 80 He has instructions to increase this dose in the face of infections or other forms of stress Histological features of the second adrenal removed which weighed 10 grammes were as follows The cortical cells are enlarged and show a particularly granular appearance Many cells show a positive reaction with Ponceau 2R There is also a profuse infiltration of round cells scattered among the other cells (George Lumb)

Comment — The most striking thing in this case was the difference at operation between adrenalectomy under cortisone cover

and adrenalectomy with DOCA and Eucortone Under corti sone the operation was as straightforward as any other routine operation and no trouble was experienced at any time The comparison between the first and second adrenalectomies was most striking

ADRENOGENITAL SYNDROME

Adrenal cortical hyperfunction when it occurs in the adult male produces in most cases the picture of Cushing s syndrome and symptoms are practically never confined to the sexual sphere When this does occur impotence and gynaecomastia are conspicuous features In girls and women however at or after puberty respectively masculinizing features such as hirsuties acne enlargement of the clitoris and amenorrhoea or irregular scanty menstruation is seen When the lesion in the adrenals is thought to be malignant surgery is indicated but an interesting use of cortisone was first put into practice by Wilkins and his colleagues (1952) who knowing that *administration of exogenous cortisone depresses production* of adrenocortical hormones put this fact to good therapeutic use In doses of cortisone sufficient to depress androgenic activity signs of virilism are suppressed The minimum dose to effect this suppression of adrenal hyperactivity is deter mined by measuring the usually markedly elevated urinary excretion of 17 ketosteroids making full allowance for the greatly varying amounts secreted in normal subjects at different ages To effect rapid adrenal suppression infants or young children are given 25 milligrams intramuscularly of cortisone daily for 7 days dosage being then reduced to the minimum effective dose perhaps 6–10 milligrams daily Children over 8 years of age are given 50 milligrams daily intramuscularly reducing in like manner after a week to the smallest effective dose In some cases injections of larger amounts every third or fourth day have proved effective Some workers have reported that when cortisone is given orally 2 or 3 times this *dosage is required given in divided doses twice or thrice in* the 24 hours If electrolyte balance is upset additional salt or deoxycortone may be necessary Wilkins and his colleagues

gave cortisone continuously from 5 to 17 months in 6 female pseudohermaphrodites whose ages ranged from 8½–18½ years Definite breast development occurred in all 6 with concomitant development of the vulva Menses have so far commenced in 3 of these patients Most of these patients showed a definite decrease in acne and hirsutism and their figures became more feminine Three had hypertension prior to therapy which disappeared while on cortisone therapy In 3 infants with female pseudohermaphrodism the effect on body growth and development when on regular cortisone dosage was observed in 1 infant 25 milligrams intramuscularly daily inhibited growth and osseous development but 5 milligrams was sufficient to suppress excessive androgen secretion without inhibiting normal growth In the other 2 infants cortisone caused no apparent retardation in growth or development It would appear that the rates of growth and epiphysial development in addition to reduction in urinary 17 ketosteroid output are important guides as to dosage inhibition of growth indicating over dosage continued excessive growth indicating under dosage

CORTISONE AND DIABETES

It was an early observation that patients suffering from diabetes mellitus who received cortisone needed in most cases a larger dose of insulin to maintain proper balance of their condition There are 1 or 2 cases on record where patients previously apparently normal became truly diabetic for the first time on therapy but to all intents and purposes it may be taken that a latent diabetes may become manifest on cortisone and a known diabetes aggravated necessitating an increase in insulin dosage the aggravation disappearing usually rapidly sometimes more gradually on withdrawal of cortisone Corticotropin (ACTH) has the same diabetogenic effect as has also growth hormone (STH) though the actions are not identical in this respect The following unusual case shows the unstable adrenocortical insulin balance which occurs in the absence of normal anterior pituitary secretion

Mrs L S now aged 46 years was a perfectly fit normal woman *until the birth of her second child on 15 11 43 by classical* caesarean section performed as an emergency for excessive haemorrhage in labour from a central placenta praevia Transfusions and resuscitation were necessary before operation could be performed A small macerated still born foetus was removed After operation her haemoglobin was 45 per cent After this her menses never returned she lost weight and complained of constant fatigue and loss of hair from head and body The pubic hair shaved for her confinement never re grew In April 1945 she developed in addition to the above symptoms polyuria and polydipsia Glycosuria and ketonuria were present and she was diagnosed after investigation as a case of diabetes mellitus given a 200 gramme carbohydrate diet and soluble insulin 15 units twice daily In September 1947 she developed *gastro enteritis and was admitted a third time It was noted* that her blood pressure was very low but that the absence of pigmentation was against the diagnosis of Addison s disease Readmitted 2 months later her blood pressure was 130/40

She was first seen by the author in March 1948 when she was admitted in hypoglycaemic coma She had taken her normal 8 units of soluble insulin in the morning and her normal breakfast but became comatose suddenly at noon She had almost recovered at 4 p m Her attentive husband then gave her the usual evening 6 units of insulin at 6 p m which returned her to coma and led to her admission to hospital She had apparently had 4 previous hypoglycaemic comas very sudden in onset and without any warning She rapidly responded to oral glucose and was fully conscious in 5 minutes Three days later her fasting blood sugar was 260 milligrams per cent post prandial 312 milligrams per cent She was discharged to the convalescent home on 6 units of soluble insulin twice daily and some days later passed again into hypoglycaemic coma at noon Dextrose 60 millilitres of a 50 per cent solution rapidly brought *her round* and she ate a hearty lunch Insulin was reduced to 4 units twice daily

In January 1951 she caught a cold Feeling faint she did not take any insulin for 3 days nevertheless she was again admitted in hypoglycaemic coma drowsy and unco operative *but rousable temperature 102 F labial herpes present (Fig 17)* The blood pressure was 90/55 The note of the Casualty Officer on duty read Please admit A case of (1) diabetes mellitus (2) *influenza* (3) Simmonds s disease She was revived rapidly by oral glucose and then received 4 units of soluble insulin from an enthusiastic staff nurse *who acted without instructions*



FIG 17 — Case L S Clinical appearance of Simmonds s disease

in as she thought the best interests of the patient This resulted in a return to hypoglycaemic coma On injection of 20 millilitres of 50 per cent dextrose intravenously she rapidly recovered before the injec tion was finished She then became entirely lucid and clear headed and gave us the history which confirmed the third diagnosis

Investigations performed in the next few days were Thorn s test which was negative x ray exami nation of chest showing old fibrotic apical disease no radiological evi dence of activity the haemoglobin reading was 96–82 per cent white blood cells 7 200 (P 87 per cent) Blood sugar on admission was 54 milligrams per cent

Plasma chlorides—440 mgm per cent equal to 75 m eq / litre (reduced)
Serum potassium—18 4mgm per cent equal to 4 7m eq / litre (normal)
Serum sodium—292 mgm per cent equal to 127m eq / litre (reduced)

Repeated 5 days later the figures were

Plasma chlorides—560 mgm per cent equal to 96 m eq / litre (normal=95–110 m eq /litre
Serum potassium—18 mgm per cent equal to 4 6 m eq / litre (normal=4–5 5 m eq /litre)
Serum sodium—316 mgm per cent equal to 138 m eq / litre (normal 140–150 m eq /litre)

Urinary ketosteroids were reduced to 1 milligram in 24 hours

Thigh neck clearance of radio iodine by the method of Foote and Maclagan was 1 6 (normal=1–8)

A repeat estimation of the urinary 17 ketosteroids showed 1 1 milligrams in 24 hours

Serum cholesterol was 212 milligrams per cent

Serum proteins totalled 6 93 grammes per cent—albumin 4 0 grammes and globulin 2 93 grammes per cent

Non protein nitrogen was 30 milligrams per cent

The Robinson Power Kepler test was positive A = 25

An electrocardiograph showed normal rhythm with low voltage curve T wave was flat in all leads

It was decided to try the effect of ACTH therapy This was given 10 milligrams 6 hourly on which she became rapidly worse with loss of appetite and a feeling of drowsiness After 48 hours her breath smelt of acetone Sugar and acetone were present in the urine in large amounts the tongue was dry and the blood pressure 75/60 At this time she was on her usual 4 units of soluble insulin twice a day ACTH was discontinued after a total of 100 milligrams had been given the patient being now almost in full diabetic coma Insulin was commenced a total of 280 units of soluble insulin being necessary to restore her to normality The blood sugar which had risen to 606 milligrams per cent gradually came down to normality

Over a period of 24 hours intravenous saline solution followed by Darrow s solution with 3 per cent glucose was given with only 5 millilitres of Eucortone into the saline drip Fourteen days later (6 2 51) she left hospital feeling better than before admission and well stabilized on 6 units of soluble insulin twice daily In the subsequent 3 weeks she felt very well ate well and gained 12 pounds in weight By March 30 she had increased a further 7 pounds in weight For 3 months after her course of ACTH energy was greatly increased She stated that she felt better than at any time after her last child birth For 2 months after the injections she felt the cold much less than previously and her appetite improved greatly Nevertheless 3 weeks after discharge she had one mild hypoglycaemic episode Insulin was reduced to 5 units twice daily but even so two further very mild hypo glycaemic episodes occurred in the following month and insulin was reduced to 4 units twice daily By May 4 3 months after her ACTH injections the effects had largely worn off and a sliding scale of insulin averaging 2 units twice daily was employed The urinary 17 ketosteroids on June 1 had risen to 4 5 milli grams per 24 hours on June 27 the reading was 3 3 milligrams

She was readmitted into hospital for review on 22 6 51 She was still 16 pounds heavier than on her previous admission and felt that she had maintained some of the improvement she had made Plasma chlorides and serum sodium potassium and cholesterol were within normal limits basal metabolic rate was –14 per cent red blood cells 4 5 million haemoglobin 89 per cent colour index 0·9 It was plain from her history that recurrent blackouts usually if not always associated with hypoglycaemia were going to be her main disability A

high calorie 2 hourly diet was instituted to combat them During periods of resting in hospital no blackouts occurred

In September 1951 she was re admitted having had four hypoglycaemic episodes in the previous few days Her condition was much as before 17 ketosteroids were 1 7 milligrams in 24 hours Insulin was re started on a sliding scale from 0-8 units twice a day depending on the amount of sugar in her urine Her manner at home was said to be strange and her husband was worried about her mental condition Although no further

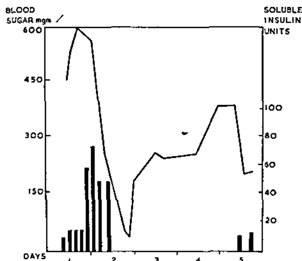


FIG 18 —Diabetic pre-coma brought on by administration of 100 milligrams of ACTH in a case of Simmonds s disease with co-existing diabetes mellitus

hypoglycaemic episodes occurred she was not in good health and appeared to be making little headway Cortisone was therefore started—12 5 milligrams a day—on 30 11 51 On this she remained tolerably well and had more energy No further hypoglycaemic episodes occurred On this dosage glycosuria is not aggravated and is easily controlled by small amounts of insulin The dose from time to time was increased to 12 5 milligrams twice a day Although she has been free from hypo glycaemic episodes she is still far from well and is now awaiting re admission for further assessment of her case

Comment—This combination of diabetes mellitus with Simmonds's disease is of course extremely rare. She had no family history of diabetes, her first child was an entirely normal one and there had been no miscarriages between the two pregnancies. As might be anticipated in the absence of a normal anterior pituitary she was extremely insulin sensitive, though this sensitivity varied considerably and in face of stress of any sort, particularly infection, she tended to pass into spontaneous hypoglycaemic coma. Minute and variable amounts of insulin were required to keep her free from ketosis and hyperglycaemia which on some occasions returned when insulin was completely stopped within a few days. On other occasions she was able to remain off insulin for 1–2 weeks without sugar returning in excess. Although she has been free from hypoglycaemic episodes since she has been on cortisone her present condition still leaves much to be desired. The chart (Fig. 18) shows the dramatic response to ACTH which precipitated her into diabetic pre-coma within a few days of her being in spontaneous hypoglycaemic coma.

CORTISONE AND THE THYROID GLAND

Cortisone has no part to play in the treatment of hyperthyroidism or hypothyroidism unless thyroid dysfunction is secondary to one of the conditions previously considered in this chapter. The effects noted both in the human and experimental animal have suggested that cortisone and corticotropin depress thyroid function but results are varying, sometimes conflicting and often inconclusive. Hardy, Riegel and Erisman (1950) found a decrease in serum protein bound iodine in 9 patients with collagen diseases in whom determination had been made before and after treatment with cortisone (2 patients) and corticotropin (7 patients). Wolfson and his associates (1950) presented evidence of depression of thyroid function in 7 patients with chronic rheumatic infection on prolonged treatment with ACTH or cortisone. In Addison's disease Perera and his colleagues (1949) and Thorn and his associates (1949) have recorded a depression of rate of uptake of radioactive iodine on cortisone therapy. In the clinical field no constant effect has been seen on thyroid activity or on eye signs.

SUMMARY

To summarize in Addison s and Simmonds s disease cortisone is a very useful substance and now constitutes orthodox therapy After adrenalectomy or adrenal destruction by disease it may be and often is life saving As a suppressive agent on adrenocortical adrenogenic overactivity it is proving its worth In the treatment of thyrotoxicosis or exophthalmic (thyrotropic) ophthalmoplegia results are too variable and inconstant to make any therapeutic claims Diabetes mellitus is aggravated inasmuch as insulin dosage has to be increased The small effective therapeutic dose in adrenocortical deficiency primary or secondary to hypopituitarism is in sharp contrast with the much larger dose used as a suppressive anti inflamma tory agent in other disorders In the endocrinological field cortisone has established for itself a secure place in therapy

F DUDLEY HART

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CHAPTER 4

RESPIRATORY AND ALLERGIC DISEASES

CORTISONE and corticotropin as has been said in a previous chapter are reported on as having a triple anti inflammatory anti allergic and anti fibrinoplastic action As most allergic lesions are inflammatory it is impossible to know in what measure the anti allergic as opposed to the anti inflammatory aspect is improved However there are cases on record (Hart Wraith and Mansell 1952) where drug sensitivity was successfully treated in the absence of inflammatory changes in such cases the action is presumably primarily a desensitizing one Where both allergy and inflammation can be combated by one drug as in allergic asthma it is natural to anticipate that therapeutic results should be satisfactory The time has not yet come which will enable us in Great Britain to state on our own experience the true value of cortisone and corticotropin in allergic and inflammatory conditions of the lung we must therefore draw in the main from American sources

ASTHMA

Rose in 1951 had treated in the previous 26 months 94 cases of asthma 72 intrinsic and 12 extrinsic (The differential characteristics are that the allergen enters the body from without in extrinsic asthma whereas in intrinsic asthma the causal factors arise within the body) Of these cases 64 received corticotropin and 54 cortisone at one time or another Many had had as many as 15 courses and some had been treated over periods of 18 months Most of the last group refused to give up treatment although in some few cases it was felt that treatment was doing little good In the very acute cases intravenous corticotropin was preferred for the less acute

cortisone by mouth or intramuscular injection As time passed more cortisone was used as it was found easier to administer and gave satisfactory results Rose found that by tapering off the dosage in older patients he could not produce longer periods of remission in the so called intrinsic group no remission lasted longer than 6 weeks In the younger extrinsic group remissions sometimes lasted up to 14 months, probably in many or most cases natural remission had occurred following therapy which may have been unrelated to the remission *In some 6 cases resistance to oral cortisone was* found even when dosage was stepped up to 400 milligrams daily for a period of 8 days Such cases occasionally responded to 200 milligrams of cortisone, intramuscularly sometimes to corticotropin

Rose attempted to determine whether prolonged adminis tration of cortisone or corticotropin for periods up to 18 months might cause deterioration in the adrenal cortex However after withdrawal of these hormones for 4–5 days he found that 25 milligrams of corticotropin given intramuscularly still produced a drop in circulating eosinophils and an increase in urinary corticoids comparable to that seen prior to treatment, and on these criteria he did not feel there was any evidence of damage to the adrenal cortex The eosinophil response to corticotropin he did not find a constant guide to effectiveness of therapy and most workers in Great Britain agree with his findings the degree of eosinophil drop in the circulating blood does not in our general experience parallel clinical improvement and in some cases satisfactory therapeutic results are obtained where Thorn s 4 hour test is negative

In Rose s total series of 138 cases there were 6 deaths 2 in status asthmaticus in spite of therapy 1 of acute broncho pneumonia Complications of therapy included instances of laryngitis and 2 cases of crush fracture of vertebrae Harvey (1951) found cortisone by mouth as satisfactory as corticotropin in relieving acute manifestations of chronic intractable intrinsic asthma if twice the dose was given Oral therapy was subsequently continued for periods up to 1 year on doses of

40–100 milligrams daily In some asthmatics the appearance of upper respiratory tract infections necessitated temporary increase of dosage and administration of antibiotics When therapy was stopped after a long period there was usually a gradual return of the asthma He saw in this series of cases no worsening of the condition following prolonged therapy and no evidence that the patients had been adversely affected Most of the patients felt that hormone therapy had been of real benefit to them

Thorn and his colleagues (1950) stated that in the majority of cases of status asthmaticus reported who had been treated at that time by corticotropin rapid and dramatic improvement had occurred within 4–36 hours of the first intramuscular injection They considered 10 milligrams of corticotropin intramuscularly 6–hourly sufficient to alleviate the average case and thought corticotropin the drug of choice in cases that had become resistant to the usual therapeutic measures Corticotropin therapy was frequently followed by prolonged remission and restoration of therapeutic effectiveness of other agents At this time however the Boston workers had had insufficient experience of cortisone therapy of severe asthma to permit proper evaluation of this hormone

Doerner and his co workers (1952) tried the effect of aerosol administration of cortisone to cases of long standing bronchial asthma which had been present 8–23 years After a preliminary control period 3 patients were given inhalations 4 times daily for 2 weeks On each occasion 1 millilitre of nebulized cortisone solution was inhaled No effect was demonstrable but on commencing cortisone in doses of 100 milligrams daily by intramuscular injection relief of symptoms began within 48 hours and was complete within 96 hours To date there are no reports on the use of hydrocortisone (compound F) by aerosol inhalation

Schwartz (1951) gave 31 courses of oral cortisone to 22 patients with chronic intractable asthma dosage being 200–300 milligrams daily for adult cases on the first day 100–200 milligrams on the second day 100 milligrams daily subsequently

until adequate relief was obtained when the dose was gradually reduced The minimum maintenance dose was usually 25 milligrams twice daily For children 25–75 per cent of the adult dose was necessary To minimize undesirable side effects all patients were given potassium iodide and a low sodium diet Symptoms were relieved in 26 of these 31 courses Five courses in 5 different patients had no beneficial effect, 4 of these patients were emphysematous Relief when obtained was in excess of that seen with previous medication and occurred rapidly within 5–72 hours of onset of therapy Symptoms returned in 61 per cent of cases within 14 days of stopping treatment there appeared to be no relationship between total dosage duration of therapy and duration of remission which varied from 12 hours to 210 days irrespective of total dosage given One death occurred in an acute asthmatic attack during the therapy after a total of 400 milligrams had been given

At the ACTH Conference held in Harrogate in 1951 in Great Britain Nattrass and Latner (1951) reported the results of a trial with corticotrophin They gave 100 milligrams daily in 4 doses to 20 asthmatics of whom 13 were in status asthmaticus the remainder though not acutely ill were subject to chronic intermittent asthma Decided improvement was noted in 9 of the 13 patients in status asthmaticus and in 3 of the other 7 cases The improvement occurred gradually over a period of 24–48 hours The dose of ACTH was usually halved after 3 days therapy In some cases a long remission resulted in others relapse set in rapidly though a second course of treatment usually resulted in a second remission Nattrass suggested that ACTH might be used when status asthmaticus does not respond to adrenaline or when previous experience suggested that other measures would be fruitless He advised that antibiotics should be given at the same time and warned against the risk of aggravating hypertension and consequent heart failure

It is well recognized that cortisone diminishes the inflammatory response to an irritant bacterial or otherwise without

necessarily affecting the causative agent In the case of infection the hormone has no effect on bacterial or viral growth and may even enhance it by removing the inflammatory process and enhancing bacterial invasiveness The experiments of Glaser and his colleagues (1951) are of great interest in this connexion They produced streptococcal and pneumococcal pneumonia in rats by intrabronchial inoculation Half the animals were treated for 5 days beforehand with cortisone the other half were untreated The survival rates in all experiments were less favourable among the animals treated with cortisone There was a striking alteration in host response to infection The lesions seen in the cortisone treated group contained excessive amounts of relatively acellular oedema fluid in which there were many more bacteria than in the lesions in analogous control animals The sparsity of cells in the oedema fluid and the extraordinarily large bacterial population appeared to be related to a delay in the diapedesis of leucocytes Cortisone *per se* was shown to exert no growth stimulating effect upon the bacteria nor did it influence significantly the phagocytic activities of the leucocytes which eventually appeared upon the scene The exact mechanism whereby cortisone depresses the process of cellular exudation which in the case of acute bacterial infections constitutes one of the principal defences of the host is unknown but these experiments point the danger of treating inflammation without also treating infection Patients on cortisone may develop respiratory infection the body response to which is damped down the clinical picture may be wholly atypical and physical signs modified or even absent In asthma therefore all workers are agreed that antibiotic therapy must be instituted at the first suggestion of intercurrent infection even if physical signs are atypical or absent antibiotic therapy may even be considered routine treatment if large doses of hormone are necessary only to be stopped when cortisone dosage is dropped to the region of 50 milligrams or less per day Merck s handbook of cortisone therapy advises that in bronchial asthma during therapy with cortisone the use of

antibiotics and other appropriate measures for intercurrent infections is essential Conventional anti asthmatic therapy should be used until the effect of the hormone becomes established Intrinsic or infective asthma as opposed to extrinsic is the more dangerous in this respect

The reports from the United States of America on the use of cortisone and corticotropin in asthma are, on the whole very favourable What is the British attitude? Although trials have not been extensive the general feeling is that cases of status asthmaticus can be considered worthy of this therapy particularly where no other previously tried remedies are of any avail where the condition is worsening or exhausting the patients and where the outlook appears grave In such cases therapy may be life saving Corticotropin given by intra muscular injection is on the whole more popular in Great Britain than cortisone by mouth or by injection in such cases action is rapid and absorption quick and certain Both substances however may be of great assistance Dosage should be gradually tapered off and antibiotics used in conjunction if there is the slightest suspicion of underlying infection or even in the opinion of many routinely

The following case history is of interest

Miss H D aged 32 years was admitted to hospital on April 21 1952 for the treatment of asthma and early cardiac failure She had been an asthmatic since childhood but was fairly free of attacks between the ages of 15 and 20 years She had gross abnormality of the chest wall having had a kypho scoliosis since childhood

She was first admitted to hospital in April 1950 and had had four or five admissions since the attacks having responded well to either adrenaline aminophylline neo-epinine or ephedrine In October 1951 she was treated with digitalis and mersalyl for cor pulmonale in addition to her anti asthmatic therapy

For the last few weeks prior to admission she had between four and five attacks of asthma a week with no true relief in between She was given mersalyl for 3 weeks for ankle oedema prior to admission

There was no family history of allergic states

Previous illnesses—Papilloma of bladder and appendicectomy

On examination—Pale wheezing pleasant person Shallow respiration rather rapid The chest wall was seen to be grossly abnormal there being a severe degree of kypho scoliosis The chest was barrel shaped Percussion note was resonant and multiple scattered rhonchi were heard Pulse was 75 blood pressure 130/80 otherwise nothing abnormal was found in the cardiovascular system Alimentary and central nervous systems were normal

On admission a diagnosis of asthma emphysema and gross kypho scoliosis was made On the evening of admission at 6 45 p m she had an attack of status asthmaticus which responded to treatment with neo epinine 20 milligrams An injection of 5 minims of adrenaline 1 1 000 was given intramuscularly and 0 24 gramme aminophylline given intravenously By 7 30 p m she was much eased

She had a further attack the following day at 4 30 p m She was then reasonably well until May 4 1952 when she had a temperature of 100 F and left sided chest pain for which she was put on penicillin She continued to have intermittent attacks though less frequently and received Pronestyl (procaine amide) 250–500 milligrams three times daily on May 12 1952 This was discontinued 7 days later as there was no marked improvement Her asthma attacks still continued and she had 10 days in an oxygen tent with slow improvement She continued to have many asthmatic attacks As her condition later became critical she was started on June 6 1952 on injections of ACTH 30 milligrams 4 times a day She remained on this drug until June 13 1952 The Thorn test at this time showed total disappearance of eosinophils after 4 hours She had much improved by June 9 had been out of her oxygen tent for 24 hours and had had no adrenaline and no neo epinine for the last 48 hours On June 12 1952 her improvement was such that she was allowed up for bed making She continued to improve despite a little left sided axillary pain and the penicillin was discontinued on June 16 1952

On June 19 she had her first attack since June 9 She was treated with 10 minims of adrenaline She had another attack which was treated with neo epinine and adrenaline subcutaneously on June 21 1952 Further progress was uneventful apart from a hysterical fit which responded well to reassurance and Gardenal Sodium 3 grains intramuscularly She had one slight attack before discharge on June 27 1952 Her condition on discharge was better than it had ever been on examination at the hospital

In some cases, however both cortisone and corticotropin fail to control the condition adequately in some there is no response at all, in some on withdrawing the drug the condition rapidly returns However these substances constitute a definite addition to our therapeutic armamentarium for a condition which annually claims a large number of victims in Great Britain In this respect the conservatism adopted is probably excessive, patients do still die in status asthmaticus who might be saved by hormone therapy The British attitude towards continued suppressive treatment of the asthmatic is at strongest, lukewarm This attitude partly arises from restriction of supplies partly from fear of infection partly from fear of abuse of the drug and partly from other factors This attitude may be entirely reasonable but reports on long term trials are still awaited Until more detailed information is available it is likely that the general feeling in Great Britain will be to restrict therapy to the acute prostrating episode which is self limiting but which may occasionally prove fatal to treating status asthmaticus when it arises rather than the asthmatic all the year round

PULMONARY EMPHYSEMA FIBROSIS AND GRANULOMATOSIS

It is impossible to subdivide cases of asthma bronchitis and emphysema adequately all co exist frequently in one patient at one time It is obvious that infection may possibly be aggravated by hormone treatment particularly when in large dosage whereas bronchial spasm and mucosal swelling is likely to be relieved A paper by Lukas (1951) is of interest in relation to the effect of corticotropin and cortisone on emphysema This author described the effect of hormone therapy on pulmonary function in 9 patients with various types of non tuberculous disease 7 of whom had considerable bronchiolar obstruction Cortisone was given to 5 of the patients corticotropin to the remainder Pulmonary function tests were carried out a short time before and on the fourth day and after 28 days of cortisone or corticotropin therapy

On therapy all the patients had some relief of dyspnoea cough and sputum production with clearing of rhonchi and lessening of wheeziness This improvement started on the second or third day of treatment and was usually maximal by the seventh day The decrease in dyspnoea was greatest in the patients who had pulmonary emphysema with evidence of considerable bronchiolar obstruction Improvement was minimal in patients without obstruction Further increase in maximum breathing capacity was seen in some cases when epinephrine was given in addition An undesirable effect noted on hormone therapy was a further depression of an already very low arterial oxygen tension and oxyhaemoglobin saturation associated with an increase in the venous admixture to pulmonary blood flow all of which findings were attributed to the development of interstitial oedema of the alveoli

It is of interest that in this work improvement occurred in cases where considerable emphysema and pulmonary fibrosis was present Lukas believes that hormone therapy exerts its good effect by exerting a sustained broncho dilating action and also believes that corticotropin and cortisone were an aid in determining the true extent to which functional impairment of the lungs could be attributed to bronchiolar obstruction rather than to permanent anatomic changes He does not anticipate that the hormones will be helpful in degenerative or senile emphysema and warns that in patients with severe and chronic restriction of pulmonary function the possibility of accentuating acutely pre existing anoxaemia may be a distinct hazard

Gladston and his co workers (1951) treated 5 patients with chronic fibrotic lung disease with corticotropin Two improved 2 worsened and 1 remained unchanged One of the 2 patients who improved committed suicide in a depressive phase after treatment was stopped In the 2 cases which became worse the deterioration was attributed to fluid retention and aggravation of a low grade cardiac decompensation In this series the therapeutic results therefore were highly unsatisfactory

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Richards (1951) put the pulmonary diseases treated by cortisone and corticotropin into two classes those where the main respiratory difficulty is impaired aeration of the alveoli as seen in the asthma emphysema group previously discussed and those in which alveolar aeration is normal the chief defect being one of faulty diffusion across the alveolar capillary membrane usually due to a fibrous or granulomatous lesion As examples of the latter he gave Boeck s sarcoidosis beryllium poisoning and a group as yet unidentified Response to hormone therapy was frequently favourable in the granulo matous diseases as opposed to the frankly fibrous lesions an example of which was pulmonary scleroderma which responded poorly Response in the first (granulomatous) group to therapy was however extremely variable and some cases failed to respond at all West and his colleagues (1951) made studies on the effects of cortisone and corticotropin in cases of chronic pulmonary disease with impairment of alveolar capillary diffusion Previous studies by 3 of these workers had suggested that impaired alveolar capillary function was the basis of the pulmonary insufficiency observed The 3 patients studied had pulmonary fibrosis due to scleroderma an unknown granulomatous lesion and one of unknown cause The first patient was not benefited by therapy the last was strikingly improved The authors speculate on the effect of treatment on a hypothetical highly vascular granulomatous process in the lung reduction of which might have resulted in lessening of the impairment of gaseous diffusion across the alveolar capillary membrane

Of this group of granulomatous alveolar capillary obstruc tion the author has no experience and there is no published work in Great Britain to date It would appear unlikely on the face of it that chronic fibrous pulmonary disease should respond unless bronchial obstruction by spasm and mucosal swelling were superadded In cases of silicosis there would be a risk of flaring up an underlying tuberculous lesion

Keeton and his colleagues (1951) reported 2 cases of bronchitis with lung fibrosis where sudden withdrawal of corticotropin treatment produced dramatic and unpleasant effects in spite of the fact that in 1 case control injections of an inert substance were substituted These cases were however, not simple bronchitis, one had developed cor pulmonale the other emphysema The second case is worth quoting A 50 year old man with chronic bronchitis and emphysema of 10 years standing was becoming progressively more dyspnoeic Corticotropin was commenced dosage varying from *40 to 60* milligrams a day Over a 45 day period improvement was slight, 72 hours after sudden and complete withdrawal of the drug he became weak and very dyspnoeic His condition rapidly worsened and by the fourth day he needed continuous oxygen By the eighth day his condition was critical On restarting corticotropin his condition improved and in 3 days he was as he had been prior to withdrawal of the hormone The drug was then gradually withdrawn over an 18 day period without incident

It has seemed to the author that most of the relief in hormone therapy in cases of so called bronchial spasm with or without chronic underlying pulmonary disease lies in reduction of mucosal swelling and restoration of a reasonable airway rather than reduction of any actual spasm Of the bronchoscopic findings during an acute attack of asthma the rapid mucosal inflammatory swelling is the outstanding one the bronchoscope being grasped by thickened swollen mucosa which protrudes over the end of the instrument and narrows the airway to a mere slit The reduction of this swelling seems to be the most likely of the various therapeutic effects possible and this may be borne out by the repeatedly seen efficacy of hormone therapy in adrenaline fast cases The chronic cases quoted above do however give the reverse of the picture and point the possible risks As many severely ill patients with asthma are of an age where cardiac decompensation is present salt restriction should always be practised and a close watch kept on the cardiovascular system Cortisone is safer than

corticotropin in such cases as it is less likely to cause salt and water retention

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Sarcoidosis so closely resembles pulmonary tuberculosis that where the diagnosis is doubtful the same risk would exist *The future in this field does not seem nearly so promising* as that in Richard s first (asthma emphysema) group

Dosage

For treatment of the acute prostrating case of status asthmaticus the correct dose of corticotropin is that which works Failure to respond may be due to inadequate dosage The usual treatment is by 6 hourly intramuscular injection If response is poor or absent dosage may be increased to the therapeutically effective level even if it be 400 milligrams in the 24 hours dosage being then reduced as rapidly and as safely as possible step by step In most severe cases however, 25 milligrams 6 hourly is usually adequate as an initial dose for example

25 mgm	every 6 hours for 2–3 days	
20 mgm		2 days
15 mgm		
5 mgm		

Such an 8–9 day course will cover most acute episodes though smaller doses are frequently effective, such as 10–12 5 milligrams 6 hourly for 10–14 days In children 5–10 milligrams *may be given 4 hourly though larger doses may be necessary* in more extreme cases of status asthmaticus Intravenous therapy produces much greater adrenocortical stimulation in smaller doses such as 20 milligrams given over an 8 hour period by intravenous infusion but in most cases of pulmonary disease the intramuscular route is less disturbing and is to be preferred also in such cases loading the circulation with extra fluid may prove harmful McCombs (1952) prefers a long acting preparation of corticotropin in gelatin finding it effective in smaller dosage Using cortisone by mouth the same general rules and dosages apply an average oral dose being

Day I	50–75 mgm	every 6 hours
Day II	25–50 mgm	
Day III	25 mgm	

dose being then gradually reduced to the smallest effective maintenance dose usually 25 milligrams 12–hourly In severe cases the Day I dosage should be maintained until relief is obtained Generally speaking both with corticotropin intra muscularly and cortisone by mouth regular spacing of dosage at frequent intervals such as 6–8 hourly is preferable to larger doses with longer intervals between As noted above close watch has to be kept on the heart in certain cases and salt restriction is often indicated Antibiotics are frequently if not always indicated in short term therapy Response to treatment will usually occur within 48 hours of starting therapy relapse will usually set in a few days after stopping it though prolonged remission may occur The duration of treatment will depend on the individual case but about 10–14 days with gradual reduction of dose after the first 2–3 days usually suffices to cover the acute episode As stated above opinion in Great Britain as to the real value of prolonged suppressive therapy is unfavourable although reports of long term trials are not available

PULMONARY TUBERCULOSIS

Attention has been drawn to the fact that cortisone and corticotropin may remove signs and symptoms of inflammation without affecting the underlying infective organism whether it be the streptococcus pneumococcus virus of poliomyelitis or smallpox or the tubercle bacillus Great care must always be taken in making careful search for active or even apparently quiescent tuberculous lesions in the patient before starting hormone therapy Although concurrent antibiotic therapy (streptomycin and *para* aminosalicylic acid) may be given in such cases where hormone therapy is strongly indicated it is safest in practice to look upon the presence of active or question ably healed tuberculosis as an almost absolute contra indication to this hormone therapy X ray examination of the chest should be made routinely in patients treated by corticotropin or cortisone over long periods It has been suggested that the inflammatory tissue response to the invasion of the tubercle bacillus is not entirely to the advantage of the host and

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severe cases of poison ivy dermatitis resistant to previous therapy have also been recorded as responding to cortisone Atopic dermatitis is said to respond occasionally dramatically In Great Britain opinion is against treating mild long lasting conditions such as allergic rhinitis with what is a short acting suppressive therapy but self limiting acute prostrating diseases such as severe serum sickness may be considered worthy of trial The author has been impressed by the relief obtained with both cortisone and corticotropin in treating and preventing transfusion reactions and uses one or other drug prophylactically in those cases who needing many transfusions are known invariably to react to them The reaction though not abolished is largely suppressed and the patient spared unpleasant symptoms is duly grateful Cases of drug allergy have already been referred to the author has seen one case where it was life saving

Harvey (1951) using oral cortisone has treated 15 reactions to penicillin 10 to tetanus antitoxin 3 to corticotropin (cases of sensitization to corticotropin have been reported cortisone has not to date induced allergic reactions) 2 to gold 1 to sulphonamides and two febrile responses to *para* amino salicylic acid All these cases were severe and had failed to respond to antihistaminics and epinephrine The initial dose given varied from 50 to 200 milligrams depending on the severity of the condition duration of therapy averaged 3 days the average total dose being 760 milligrams The usual course was an initial dose of 100 milligrams followed by 50 milligrams 4 hourly for 6 doses then every 6 hours for 4 doses Rapidity of response to therapy was striking and he states these conditions form a very practical and well documented use for cortisone Furthermore the response of the cutaneous manifestations to the oral administration is so prompt that one can get a fairly clear titration of the effective duration of a single dose Effects could be seen to come and go within the 4 hour spacing of dosage

Looking over the long list of allergic conditions which have been treated by cortisone and corticotropin although

that modification of it by hormone therapy might be of use in therapeutics Although some favourable results have been reported in the main they have been disappointing for though the patient might feel better and fever abate there was little evidence that the course of the disease had been altered Slight radiographic changes were reported and there was rapid decrease of laryngeal oedema in patients with tuberculous laryngitis but changes were transient and did not persist after treatment was discontinued As noted above animal work points entirely the other way and shows that these hormones may intensify the process of infection Cortisone treatment of guinea pigs and rabbits with acute tuberculosis causes extensive and widely disseminated lesions and the effect though lessened is not abolished by streptomycin and P A S Hart and Rees (1950) found that in mice the course of experimental chronic pulmonary tuberculosis was definitely altered for the worse by cortisone proliferative lesions enlarging and becoming necrotic and the number of bacilli in them increasing Several cases of activation of previously apparently quiescent tuberculous disease in man have been reported and there seems little doubt that the presence of tuberculosis as noted above in active or doubtfully quiescent phase should be an almost absolute contra indication to cortisone or cortico tropin therapy Tuberculosis is a killing disease most of the diseases at present treated by cortisone are not

ALLERGIC DISEASE

The place of cortisone and corticotropin in the treatment of asthma has been discussed above in the United States of America a large number of other allergic conditions have been treated and success claimed in angioneurotic oedema atopic dermatitis exfoliative dermatitis including cases resulting from drug allergy and many others Symptomatic relief has been obtained with lessening or disappearance of the physical signs In some conditions such as severe exfoliative dermatitis it is possible that a fatal outcome has been prevented in some cases Relief has been reported in contact dermatitis and

CHAPTER 5

SKIN DISEASES

WHEN in 1947 the publication by Hench and his colleagues (1949) of the news that the administration of Kendall s com pound E exerted a profound effect in modifying the course of cases of rheumatoid arthritis, it was hoped that these hormones would provide us with new and extremely powerful therapeutic weapons

It was not long however before it was realized that this early promise would not altogether be fulfilled for while there was frequently a dramatic change in the symptoms and signs of disease the tendency to relapse on withdrawal of the drugs indicated that the underlying pathology remained essentially unchanged

It is known of course that the main function of the adrenal cortex is to enable the body to maintain its metabolic equili brium in the face of internal and external changes in the environment There is as yet no clue as to the way in which this function is accomplished by the hormones of the adrenal cortex but their action must be exerted by modifying metabolic processes without taking any part in initiating or stopping them

Thus we can see that cortisone and ACTH cannot cure disease or directly influence its pathology but they appear to act by diminishing the response of the tissues to injury Therefore in the case of certain diseases such as the more chronic forms of pemphigus vulgaris for example it is hoped that by enabling the patient to successfully resist and survive exacerbations of the disease progress life may not only be greatly prolonged but may be prolonged sufficiently for the underlying pathological process to undergo possible sponta neous resolution in the course of time

most are merely disagreeable and troublesome some may on occasion be dangerous to life itself Such potentially fatal diseases, which are self terminating can be 'tided over with hormone therapy, which has a real place in the treatment of such conditions Dosage is as outlined under the treatment of asthma shorter 4-hourly spacing being used in drug sensitivities as described by Harvey

F DUDLEY HART

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of life the saving of sight and the prevention of crippling Pickering and Lovell of the Medical Unit very kindly considered the pros and cons of treatment of many cases for the author some of which are recorded in full In addition Brooks and Lichfield shared the therapy of a number of patients Guided by these principles and controlled by the stocks and prospects of supply it was possible to save a number of patients from death and crippling Several patients made only temporary improvement and it is possible that this new and powerful therapy may have hastened the end of at least one A number of these cases are recorded *in full as the author feels that many lessons are to be learnt* and the tremendous importance of investigations in the initial stages in hospital and near a laboratory can be seen Continuous nursing and medical care are also necessary and only when assured of such assessment and care should *outpatients be recipients of such treatment*

At the Tenth International Congress of Dermatology in London the problems of the effects of cortisone and ACTH on the skin and its diseases were fully discussed Admirable opening papers were read by Brunsting (1952) Sulzberger (1952) and Ereaux (Browne and Ereaux 1952) Many of their observations have been included in this chapter Brunsting pointed out that the mechanism of action by which cortisone and corticotropin influence the symptoms and course of certain non hormonal diseases in man and animals is still obscure There is no clue in the known physiologic effects of these hormones on the metabolism of carbohydrate nitrogen fat or electrolytes even when these effects are exaggerated through overdosage Cortisone and corticotropin do not cure disease by the eradication of the cause nor do they repair damaged tisue Their chief therapeutic value lies in their capacity to act as buffers to the reaction of tissues to injury particularly tissues of mesenchymal origin as well as to block reactions to allergy and hypersensitivity Unfortunately in the case of infection in which the injurious agent is microbic such effects may be detrimental to the patient

This modified view of the therapeutic value of these hormones necessarily leads to some change in the attitude towards their field of most useful application

This change of outlook is well reflected in the field of hypersensitivity and allergy where ACTH and cortisone have a marked action in reducing the effects of reactions of hyper sensitivity on the tissues although the actual interaction of antibody and antigen proceeds unchanged Thus for example there is a great tendency today to use these drugs to suppress the immediate ill effects of self limiting conditions such as say, a severe contact dermatitis until the disease process naturally subsides

Although it is with considerable caution that we view the use of substances which are capable of exerting as profound bodily effects as are cortisone and ACTH there is a great deal of evidence to support the view that in short courses and in moderate dosage the danger of ill effects is almost negligible providing all the normal precautions attendant always upon the use of these drugs are taken When long courses are given or when maintenance doses are continued for long periods of time there is much evidence to suggest that serious ill effects may ensue in some cases Before one recommends such long continued doses for other than the most serious conditions one will wish to see a good deal more evidence than at present exists regarding this aspect of therapy and this despite the fact that there is some support for the view that if the doses are so small as to cause no obvious physiological side effects they are likely to be harmless

Since 1949 the influence of ACTH and cortisone has been studied far and wide in the United States of America Supplies were imported into Great Britain but the restriction on dollar spending necessitated a rigid control Certain departments of medicine had limited quantities of this precious remedy At first the right of prescription was limited to a few physicians for only a certain number of diseases At St Mary s Hospital it was agreed that the highest priorities should be the saving

The effects of cortisone differ slightly from those due to ACTH in that they seem to be more variable and in many instances lesser in degree

In both instances however there is a marked initial retention of sodium chloride and water followed after a variable period of time which may often be as short as a few days by an increased excretion of sodium and chloride ions and also water with a subsidence of oedema

These effects are minimal where cortisone is the drug used and the dosage is not more than 100 milligrams daily other factors being equal (Sprague and his colleagues 1950)

Potassium excretion

Potassium excretion is increased considerably and in some cases the serum levels may fall so low as to cause an alkalosis If this is combined with the increased excretion of sodium and chloride which often follows the initial retention of these ions the state of affairs may be further exaggerated producing a hypopotassaemic and hypochloraemic alkalosis

In the majority of skin patients this salt and water retention leads to little more than a moderate weight gain and even the appearance of slight oedema although even these effects are not likely to be seen if the course is short the dose relatively small and the intake of sodium chloride restricted In some cases however almost invariably those with severe systemic diseases such as acute disseminated lupus erythematosus or pemphigus these effects in the face of probable renal and cardiovascular damage have led to congestive cardiac failure and pulmonary oedema There is also a rise in the systolic and diastolic blood pressures in some cases during the administration of the hormones but this occurs much more frequently in the acute disseminated lupus erythematosus than other conditions due probably to the high incidence of severe renal damage (Sprague 1951) when added to the effects of fluid retention it may however help to induce cardiac failure This problem is further dealt with in the section on acute disseminated lupus erythematosus It is evident therefore that with the exception of severe and fatal diseases such as

These writers have felt that the disease process continues beneath the surface like a subterranean river (Sulzberger 1952) or an 'iceberg in the sea (Browne and Ereaux 1952) until the normal processes effect a cure or the reaction to an irritant no longer in action has subsided

PHYSIOLOGY—COMPLICATIONS

In addition to their effects upon disease, these hormones have very marked physiological actions many of which are undesirable

In order therefore to be in a position to use ACTH and cortisone with safety an intimate knowledge of these processes is necessary

Although some effects to be discussed are not likely to occur with the dosages normally used in the treatment of disease many of them are constant accompaniments of even average therapeutic doses In addition in grave diseases such as for example acute disseminated lupus erythematosus, when there are often profound disturbances of function in various bodily systems such as the renal and cardiovascular systems any side effects involving these might be considerably exaggerated

It is therefore proposed to give a brief account of the physiological effects of the drugs and the side effects and complications to which they may give rise before discussing their value in various dermatological conditions

Two of the most important groups of effects from the therapeutic standpoint are those affecting electrolyte metabolism and those affecting organic carbohydrate protein and fat metabolism

Electrolyte metabolism

Although their capacity in this respect is vastly smaller than that of desoxycorticosterone acetate there is no doubt that both these hormones may cause a retention of sodium and chloride and water even on the dosages used therapeutically

However as might be expected these physiological effects become extremely important when treating patients with diabetes It has been observed that in the case of such patients the previous insulin requirements may be doubled during administration of the hormones or cases which previously required no insulin now exhibit greatly increased glycosuria hyperglycaemia and ketonuria

There is some evidence to suggest that these effects in patients with diabetes are due to the loss of islet tissue whereas in normal patients with a large functional reserve presumably increased production of insulin is able to cope with the abnormal state of affairs produced by the drugs Sprague noted that 2 of 4 patients who showed some degree of carbohydrate intolerance while on cortisone had a family history of diabetes

However provided the condition is watched very closely diabetes does not constitute a contra indication to the use of the hormones

Infections

It is now well known that while cortisone and ACTH will suppress many of the symptoms and signs of a bacterial infection the course of the progress is unchanged It appears that the power of reaction of the tissues to the noxious agents in this case bacteria is inhibited while the organisms continue to flourish unaltered This observation is of profound importance in the management of patients under treatment with these hormones for the signs and symptoms of intercurrent infections will be largely suppressed Thus peritonitis abscesses (especially gluteal) pneumonia and septicaemia have all arisen during treatment and in many cases the characteristic signs and symptoms have been so lacking as to make diagnosis difficult or impossible so that the patients have died with the complication unsuspected

However small pointers are often present such as slight abdominal pain or increase in temperature or pulse rate and with increased awareness of these dangers they should arouse suspicions and coincident with immediate investigations

pemphigus and acute disseminated lupus erythematosus the presence of hypertension cardiac or renal disease constitutes a contra indication to the use of the drugs

The potassium thus excreted is derived partly from protein breakdown and partly from extracellular sources (plasma) and it has been found that the administration of testosterone propionate with cortisone and ACTH reduces the rate of excretion considerably by preventing much of the excessive protein metabolism but does not prevent the excretion of that potassium which is derived from the blood plasma

Nitrogen excretion

This increased protein breakdown leads to a negative nitrogen balance although once again this effect is only seen when the hormones are administered in relatively large doses This increased loss of nitrogen can be minimized in more than one way however Thus by concurrently administering testosterone as already mentioned it is largely abolished A similar effect has been achieved by doubling the amount of protein in the diet or more simply still by increasing the intake of potassium This latter observation is probably the most useful from the clinical point of view since it has the merit of also correcting the hypopotassaemia which would be present

This increased nitrogen loss is also associated with an increase in uric acid excretion although the serum levels of uric acid may or may not be unchanged

Carbohydrate metabolism

Although the administration of large doses of cortisone and ACTH to experimental animals has resulted in a diabetic state with glycosuria hyperglycaemia ketonuria and changes in the islet cells the effects produced on patients with previously normal carbohydrate metabolism are relatively slight Thus little more than glycosuria and mild hyperglycaemia are produced even with moderately high doses Indeed the minor degree of elevation of blood sugar in some instances has led to the suggestion that the glycosuria may be largely due to a lowering of the renal threshold (Conn Louis and Wheeler 1948)

may cause gastro intestinal ulceration and haemorrhage Thus cases have been recorded in which perforation of peptic ulcers has revealed at autopsy that the ulcers were acute with little evidence of fibrosis (Beck and his colleagues 1950, Habif Hare and Glaset 1950) In addition these patients had no previous ulcer history Likewise haemorrhage has been observed (Sprague 1951) Such reports prove nothing since acute peptic ulcers particularly acute duodenal ulcers are well known to arise during other diseases—severe burns and surgical procedures—but this in itself argues slightly in favour of incriminating ACTH and cortisone since these are all situations of great stress in which the level of circulating corticosteroids may be presumed to be high

Furthermore there is strong evidence suggesting that ACTH and cortisone and particularly the former actively retard the healing of peptic ulcers or even activate them (Forbes 1952) Thus peptic ulceration should be considered a relative contra indication to the giving of these hormones and in cases in which they are considered vitally necessary an extremely careful watch should be kept for the slightest signs or symptoms of worsening of the gastro intestinal condition always bearing in mind that these may be largely suppressed

Nervous system

Although mental changes are not seen infrequently during the administration of ACTH and cortisone these changes have in general been more severe in patients with severe systemic diseases

Thus while mild changes such as sleeplessness anxiety and euphoria are very common more severe ones such as manic and depressive states or schizoid psychoses are far less common and probably represent an intensification of an already abnormal personality with a family history of psychosis and these are unsuitable subjects (Rome and Braceland 1950)

Where psychotic episodes appear and the continued adminis tration of the drugs is vital treatment by electro shock may be followed by a return to normal while the hormones continue to be administered

which should always include x ray examination of the chest full antibiotic therapy should be commenced

In addition to the paucity of symptoms and signs the effect of the drugs in *causing a leucocytosis in many patients means* that this investigation is of little diagnostic value Thus if a *patient has or has recently had an infection this constitutes* a contra indication to the drugs

Chest diseases

In addition to the infections already mentioned tuberculosis is a special danger for there is much evidence to support the view that the drugs may cause serious exacerbations Thus while actual proof is lacking reports such as those of Hulbert (1952) who describes the onset of miliary tuberculosis in a patient with a normal chest radiograph prior to treatment and of Prunty (1952) make it imperative to exclude the disease before starting therapy and make the presence of tubercle bacilli an absolute contra indication to the use of the drugs A possible exception might be the onset of acute disseminated lupus erythematosus in a patient with tuberculosis in whom one might be forced to give ACTH plus appropriate chemo therapy as a measure of desperation

In addition to infection the healing of wounds can be delayed owing to the effects of the hormones on mesenchymal tissues

Hypothyroidism

There is some evidence although it is as yet by no means conclusive that the administration of ACTH and cortisone for long periods of time causes a depression of the thyrotropic function of the anterior pituitary This has been advanced as an explanation of the fact that some conditions which responded initially to the hormones suddenly cease to do so after being maintained on them for a long time *It is further* stated that this state of unresponsiveness can be overcome by the administration of thyroid extract

Gastro intestinal

There is to date a considerable volume of evidence even though it is mainly circumstantial that ACTH and cortisone

regular estimation of circulating eosinophils in the blood would seem to be unnecessary except where specially indicated since an adequate clinical response to the drugs can occur even in the absence of such a lowering

If the course of treatment is likely to be lengthy and the dosage high the urinary nitrogen excretion should be estimated and the bones examined radiographically This latter pre caution should always be undertaken before treating children in view of the known detrimental effects of cortisone and ACTH on osteoblastic activity and chondrogenesis

During therapy fluid intake and output blood pressure and urine examination should be estimated daily while a blood count and blood chemistry should be repeated weekly Should glycosuria be noted a blood sugar examination and sugar tolerance curves must be done and diet and insulin administered if necessary

If patients receive the drugs for more than a week intake of salt should be restricted to 2 grammes daily and potassium chloride 2–5 grammes daily given by mouth

Increased nitrogen excretion can be countered by adminis tration of testosterone propionate

In some cases after prolonged administration of the drugs a patient may suddenly fail to respond to the dosage being given and there is some evidence to suggest that this may be due to inhibition of thyrotropic hormone due to pan pituitary depres sion since administration of thyroid extract will correct it

Water retention may be controlled by salt restriction or in some cases may necessitate the administration of mercurial diuretics While intercurrent infection either proven or suggested perhaps by lack of response to the drugs by raised pulse and respiration rate and temperature or other unexplained signs calls for immediate antibiotic therapy

Patients on maintenance doses of the drugs should have monthly examinations of the blood and serum chemistry bleeding and coagulation times as there tends to be a re duction in the coagulation time during the administration of these drugs skiagrams of the chest and of the bones should

Convulsive seizures have been observed but the majority have been in cases of acute disseminated lupus erythematosus where such symptoms are not unknown in untreated cases

Osteoporosis

As in severe cases of Cushing s disease osteoporosis and spontaneous fractures may result from prolonged therapy with ACTH and cortisone but only if the dosage is relatively high Teicher and Nelson (1952) describe a case in which there was collapse of the vertebrae from Th 9 to L 5 This progressive osteoporosis was unaltered by the administration of calcium and testosterone

Other minor side effects

Other minor side effects which are seen during hormone therapy are facial rounding (the moon face) acne hirsutism atropic striae amenorrhoea and menorrhagia These are most likely to occur in adolescent girls and menopausal women

An increase in the pigmentation of the skin either as a darkening of pre existing freckles or lentigines or a more generalized brownish pigmentation is sometimes seen (Rosenberg and his colleagues 1951) The majority of these complications diminish or disappear when therapy is stopped

PRECAUTIONARY MEASURES TO BE OBSERVED BEFORE AND DURING THERAPY

In view of the physiological effects of these drugs many precautions should be attendant upon their usage

First a careful history taking is essential particular emphasis being placed upon a past evidence of diabetes hypertension cardiac disease other thrombotic phenomena mental instability peptic ulceration tuberculosis or any other infection The family history may also be of some significance

A complete general examination including chest x ray examination blood count urine examination weight taking and consideration of the blood pressure plasma sodium potassium and carbon dioxide combining power should also be undertaken before therapy is started in every case The

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be taken if indicated while weekly examinations of weight, urine blood pressure and emotional state should be carried out These points are shown extremely clearly and well in Sulzberger s Table (1952)

TABLE

PRINCIPAL MEASURES TO BE INSTITUTED IN PATIENTS RECEIVING CORTISONE OR ACTH (*Sulzberger 1952*)

Examination before instituting therapy	Examinations weekly during therapy	Examinations monthly during therapy	Procedures to prevent or counteract ill-effects
Complete history and studies with special reference to diabetes hypertension thrombotic or haemorrhagic states psychosis psychoneurosis active tuberculosis or other occult infection peptic ulcer	Weight blood pressure routine urine and blood count psychic and emotional state	Blood counts including circulating eosinophils bleeding and blood clotting factors urinary steroid excretion blood chemistry for sodium and potassium levels etc roentgenograms of bones (as required, e g in children)	Low salt added potassium and as needed thyroid insulin antibiotics testosterone diuretics etc

Dosage

An attempt to arbitrarily decide suitable dosages of these drugs in any given condition must necessarily be very approximate since they may be compared to insulin in that the correct dose must be determined in each individual Some recommendations to provide a rough base line for commencing and continuing treatment may however be of value

The different methods of administration of the drugs are as follows ACTH which is a protein substance and therefore can only be administered parenterally is given either as an intramuscular injection every 6–8 hours, or as an intravenous infusion in 500 millilitres of 5 per cent Dextrose given over 8 hours There are also preparations of ACTH gels becoming available which have a longer action, but relatively little is yet known of these Cortisone may be given intramuscularly once daily, or by mouth every 6–8 hours

It should be pointed out that 3–4 times as much cortisone is required to equal a given dose of ACTH by intramuscular injection while continuous intravenous infusions of ACTH are up to 10 times as effective as a similar dose of cortisone the maximum daily dose by this route seldom exceeding 25–30 milligrams ACTH gel preparations occupy an intermediate position between the two The dosage of the hormones varies in different conditions and in different individuals but dermatoses may be roughly divided into those which are severe and often fatal such as acute disseminated lupus erythematosus pemphigus dermatomyositis and exfoliative dermatitis and all others In the first group dosage generally is considerably higher than the second and has been dealt with in some detail under these diseases In general however, the initial doses of the drugs should not be less than 100–300 milligrams of ACTH or 200 up to even 1 000 milligrams of cortisone daily Some observers favour starting with the smaller dose and increasing it if necessary until there is a therapeutic response while others favour starting with a large dose preferably of cortisone say 300–500 milligrams and reducing as necessary (Ereaux 1952) There would seem to be little to choose between either of these methods except to remember that in severe conditions the dose of the drug should be increased until a therapeutic response is obtained other things being equal When very large doses have been prescribed as in the crisis of acute disseminated lupus erythematosus they may be given as often as every 2–4 hours for a day or two Under these circumstances cortisone by mouth is probably the drug of choice since its action is rapid but short lived thus enabling the dose and the effects of the drug to be rapidly adjusted in the face of clinical response or the onset of severe complications

For less severe dermatoses the average initial daily dose of cortisone varies from 50 to 75 milligrams in infants and children up to 150–200 milligrams for adults Equivalent doses of ACTH by intramuscular injection are roughly 20–100 milligrams

Once the correct initial dosage has been found by the response of the disease it is maintained until the symptoms and signs have been fully suppressed It will then be necessary *either to withdraw the drug altogether or, if the condition* warrants it reduce the dosage until the minimal dose which just suppresses symptoms is found This tapering off of dosage is done by reducing the dose first by 25 milligrams every 3 days until it is reduced by half and then 12 5 milligrams daily until the correct maintenance dose is found or the drug is withdrawn This question of the safety or otherwise of long continued maintenance doses of the drugs is not yet decided and in general it would seem wise not to give them *for long periods of time in any but the most serious diseases* until more information is available It may be true however, that provided the maintenance dose is low enough to avoid giving rise to any physiological side effects there will be no danger

When cortisone is withdrawn especially if the withdrawal has been too sudden there is often a period lasting a week or more, during which the patient may experience unpleasant symptoms of adrenal depression such as tiredness and muscular *weakness or more unpleasant and even dangerous an* exacerbation of the disease which may become worse even than it was initially In an effort to offset this some authorities have suggested substituting ACTH for cortisone just before stopping the drugs but there is as yet no real solution to this problem The dosage of the drugs may have to be increased in the presence of an intercurrent infection to produce the same effect as before should it be necessary to continue them together with antibiotics

As to the relative effectiveness of the different forms of the drugs provided that relatively equivalent doses are given and the adrenal glands are intact there is nothing to choose between cortisone and *ACTH most earlier reports stating that one* was slower acting than the other or less efficient were due to the doses not being comparable

It is possible that the giving of ACTH, by intravenous infusion may be the most effective as well as the most econo mical method of all in short term cases It has the disadvantage however of often causing venous thrombosis as well as being more troublesome to administer

The dosage of the drugs required by infants and children is greater weight for weight than that required by adults

ACUTE DISSEMINATED LUPUS ERYTHEMATOSUS

When the treatment of this condition was first begun with cortisone the preliminary results suggested that here at last might be the answer to this condition

This hope has only been partially realized however The severe and irreversible systemic damage caused by the disease particularly to the renal and cardiovascular systems together with the realization that ACTH and cortisone do not affect the underlying fundamental pathological processes mean that any improvement which results from therapy is likely to be temporary

The treatment of acute disseminated lupus erythematosus with these drugs resolves itself therefore into two main phases the first being the suppression of the signs and symptoms of the disease process and the second the maintenance of the remission thus produced and the treatment of relapses should these occur In this last respect one of the most important situations likely to arise is the lupus erythematosus crisis—a fulminating state of affairs which is fortunately relatively uncommon A number of the earlier reports which have been published dealing with ACTH and cortisone treatment of this condition concerned cases many of which were extremely severe with gross structural changes or almost moribund In many instances the dosages of the drugs used were lower than are being used today in the light of experience It is unnecessary here to more than briefly mention some of the most important and typical clinical features of the disease such as the fever arthritic symptoms eruptive phenomena renal and cardiac changes serous effusions and cachexia

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and pericardial effusions and friction rubs although pleural pain itself may persist (Brunsting and his colleagues 1951) The cutaneous lesions are somewhat slower to resolve and their rate of disappearance would seem to depend as one might imagine mainly upon their initial severity Thus erythematous lesions fade in 2–4 weeks whilst ulcerations take somewhat longer Lesions of the mucous membranes however resolve fairly rapidly and have healed within 7–10 days Unfortunately these effects are all temporary and relapses occur after varying periods of time once the drugs are stopped The problem of maintaining a remission once it has been achieved will be considered later when discussing dosage

Effect of the drugs on biochemical and pathological findings

The results of treatment as gauged by its effects on laboratory data are extremely disappointing They merely serve however to emphasize that ACTH and cortisone do not affect the basic pathology of disease but merely suppress its symptoms and signs

The anaemia is generally uninfluenced by therapy although some improvement has been reported (Brunsting and his colleagues 1951 Adlersberg Schaefer and Drachman 1950)

They reported that though the numbers of leucocytes fluctuated fairly widely from time to time leucopenia generally tended to improve without being entirely abolished except in a small proportion of cases

The changes exhibited by the serum proteins are variable and although in some cases there has been a lowering of the globulin fraction thus tending to shift the abnormal albumin globulin ratio so characteristic of the disease towards normal the improvement has been relatively slight The albumin as a rule has exhibited little change The findings of Soffer and his colleagues (1951) were not in accordance with this view however since they found that the serum globulin values fell almost to normal during treatment

The effect of ACTH and cortisone on the sedimentation rate varies and while in some cases it appears to be unin fluenced by the drugs even when a clinical remission has been

Among the biochemical and pathological abnormalities the most important is the lupus erythematosus cell while other typical changes are albuminuria urinary red cells and casts anaemia leucopenia, elevated blood sedimentation rate and changes in the plasma proteins

Effects of drugs on signs and symptoms

The effect of both ACTH and cortisone on the signs and symptoms are identical except that cortisone takes longer to produce a clinical response than ACTH unless it is given in relatively higher dosage (Haserick 1951) Also the effects of ACTH wear off less rapidly than those of cortisone when the drugs are stopped although Soffer Levitt and Baehr (1950) considered that the converse was true

All observers are agreed that the first response to treatment is a fall in temperature This usually takes place within 1–4 days soon attaining normal levels Failure to reduce the *temperature has almost invariably appeared to be the result* of too low a dosage as for example in one of the cases of Brunsting and his colleagues (1951) where a dose of 100 milligrams of cortisone daily failed whereas 200 milligrams daily succeeded in reducing the temperature to normal levels Failure to reduce the pyrexia in the absence of other causes of pyrexia such as intercurrent infection or failure to bring other symptoms under control should at once raise the question of the adequacy of the dose since this varies from individual to individual and according to the severity *of the disease process This important question will be dealt* with further when discussing the treatment of acute crisis with massive doses of the drugs Rapidly following the fall in temperature comes the disappearance of tachycardia and of more severe cardiac manifestations such as gallop rhythm Other features which are usually normal by the end of the first week include joint pains and stiffness Malaise gradually disappears and the profound feeling of weakness and fatigue which is common to the disease steadily gives way to increasing strength within 10 days or so Other clinical features which resolve *during the first 2 or 3 weeks of therapy* are pleural

of instances treatment does cause some reduction in the numbers of lupus erythematosus cells to be found on any one occasion although the alteration is purely temporary

Dosage

Although some authors have stated a preference for one drug rather than the other in general either ACTH or cortisone seems equally effective provided that the dosage is adequate Some earlier observers preference for one drug rather than the other was probably due to failure to appreciate the greater dosage of cortisone required to produce the same effect as ACTH Haserick and his colleagues (1951) in an experience of 16 cases maintain that relapses are less severe and seem to be slower in onset in patients treated with ACTH as compared with those treated with cortisone In any case the vital need in the treatment of this condition is that the dosage be adequate initially Thus if a therapeutic response which is usually first heralded by a fall in temperature is not rapidly produced the dose should be increased until this is achieved consistent with the patient being able to tolerate it

In view of the very high incidence of complications of treatment in this disease the biochemical and other investigations should be watched most carefully in these initial stages In general however the initial dosage of ACTH should probably be between 150 and 300 milligrams and that of cortisone 300–500 milligrams

One of the most alarming features of this disease is the so called crisis a state of affairs in which the disease process is one of the utmost severity Such a state of affairs may arise for no apparent reason, or some insult such as an intercurrent infection may provoke it In any case such a factor should immediately be sought and even if not found full antibiotic therapy instituted These principles apply to any case of acute disseminated lupus erythematosus which fails to respond properly to ACTH or cortisone

Cortisone is probably the drug of choice to deal with the crisis and it should be commenced in a very high dosage and reduced as soon as a response is obtained The actual dose

induced, most observers have found that it is reduced in the majority of cases and in some instances there has been a return to normal levels (Irons and his colleagues 1951)

The abnormal renal findings remain as one would expect materially unchanged since they are merely an index of the irreversible structural damage suffered by the kidneys Thus albuminuria, microscopic haematuria the presence of casts as well as lowered urea clearance values persisted unchanged Haserick (1951) however describes a case in which there was some improvement the blood urea falling from 231 to 87 milligrams per cent and the urea clearance increasing from 7 per cent to 29 per cent

One of the most valuable laboratory aids to diagnosis is the discovery of the lupus erythematosus cell or lupus erythematosus phenomenon in the bone marrow or peripheral blood of patients with this disease, or the production of these cells in normal bone marrow by the addition of plasma from patients with acute disseminated lupus erythematosus

The cell itself is a polymorphonuclear leucocyte containing a large round usually amorphous body within its cytoplasm Similar amorphous masses may be found extracellularly and in some cases polymorphonuclear leucocytes are clumped round them in rosette formation These changes may be found even in the absence of actual lupus erythematosus cells and have the same sinister significance

Although in the vast majority of reported cases ACTH and cortisone failed to abolish the phenomenon some instances have been reported where the actual lupus erythematosus cells themselves disappeared from the bone marrow However in the case of Brunsting and his colleagues (1951) whenever this occurred it was only temporary and recurred immediately the drugs were stopped and even while the cells were not to be found the extracellular amorphous debris which is characteristic was never absent from bone marrow smears

Cases have been reported in which the lupus erythematosus cells first appeared during treatment with ACTH or cortisone (Haserick 1951) It is true to say however that in a majority

of this particular disease necessitates mention of those side effects particularly likely to be seen during its treatment

In the early stages of therapy there is usually a retention of sodium chloride and water which may lead to fluid retention and oedema This is usually reflected by a rapid gain in weight and may be counteracted to a large extent by a restric tion of sodium in the diet Some authorities recommend a salt free diet but a restriction of salt to 2 grammes daily is usually considered adequate

Cardiovascular complications

A rise in the systolic and diastolic blood pressures may occur early in treatment although the rise is usually slight in degree and rarely exceeds 50–80 millimetres of mercury and 20–40 millimetres of mercury respectively even in the worst cases This rise in blood pressure is rarely seen except in patients with acute disseminated lupus erythematosus and is thought to be due to the severe renal damage which usually occurs Slight as this rise may be taken in conjunction with possible fluid retention severe effects of the disease on the cardio vascular system as evidenced by gallop rhythm and pericarditis and damage to the kidneys it may lead to congestive heart failure (Baehr and Soffer 1950) Thus in 4 of the 14 cases seen by Soffer and his colleagues (1950) cardiac failure occurred while in 1 patient pulmonary oedema occurred on two occasions Although salt restriction minimized the fluid retention and also had some effect in reducing the elevation of blood pressure cardiac failure still occurred in certain cases In these instances the onset of failure was not accompanied by a very great gain in weight (2 or 3 pounds only) A low salt diet therefore in no way replaces the need to be constantly watching for cardiac complications These attacks of heart failure are fairly readily controlled in most cases by digitalis oxygen and mercurial diuretics while still continuing administration of the drugs Although in cases where renal damage is also severe it may be impossible to avoid the fluid retention except by stopping them The use of mercurial diuretics has certain disadvantages however for by causing an increased excretion

level is purely individual but can be best indicated by cases (*Haserick and his colleagues 1951*) The first patient had responded well to 200 milligrams of cortisone daily when on the thirteenth day she suddenly became moribund The dose was immediately increased to 50 milligrams 2 hourly and after 12 hours with some response the dosage was changed to 50 milligrams 4 hourly After a short time the patient was changed to ACTH and ultimately maintained on 40 milligrams daily

The second case was given 900 milligrams of cortisone the first day in divided doses 1 050 milligrams the following day and on the third day 2 300 milligrams before a response was obtained This was then reduced to 1 400 milligrams on the fourth day and gradually decreased

Once a remission has been induced there arises the question of maintaining it Either the drug can be gradually discontinued until the patient can finally forgo it without any recurrence of symptoms or a suitable maintenance level can be determined below which signs of activity begin to appear, and the administration of the drug continued indefinitely at this level It is in these cases that the doctor s dilemma arises How to keep up the supply But there is much to recommend this latter method as the most satisfactory one especially now that the drugs are becoming a little more plentiful

Should a relapse occur at any time the dose must be immediately stepped up as already described until the symptoms are once again under control

Complications

As already stated the widespread nature of the underlying pathological changes involving as they do almost every system in the body mean that the physiological effect of cortisone and ACTH on these systems small and relatively unimportant as they often are in the normal organism become now of vital significance and not infrequently attain menacing proportions Although the complications of ACTH and cortisone therapy in general have been dealt with elsewhere this peculiarity

confined to bed until her death from renal failure in February 1952

It is difficult to say to what extent the cortisone was responsible for these mental changes but the relationship of their onset to administration of the drug suggests that it was at least an aggravating factor

Intercurrent infections

Intercurrent infections do not present any problems peculiar to the treatment of this disease but tuberculosis deserves mention The occurrence of tuberculosis miliary or otherwise in conjunction with acute disseminated lupus erythematosus is well recognized but it is now generally regarded as not having any aetiological significance presumably the cachetic and debilitated state of the patient merely makes its supervention more likely However the experimental evidence of the harmful effects of ACTH and cortisone on tuberculosis make it advisable to make a special effort to exclude it before treatment and to suspect it during treatment Although there is no proof of the role played by ACTH and cortisone cases of miliary and active caseous tuberculosis have been reported during hormone therapy of acute disseminated lupus erythematosus (Hulbert 1952 Prunty 1952)

Mrs L T aged 35 years was admitted with a history of a rash developing on her forehead 2 years previously which had gradually spread over her face and neck the sternum and the fingers At the same time she noticed a sore mouth During this latter period she had pains in the knee hand and shoulder joints and complained of lassitude shortness of breath on exertion and nervousness in the past she had had pneumonia during World War II for which she had been given sulphonamides

On examination there was a patchy papular rash present on the forehead cheeks chin ears V shaped portion of the neck and the fingers consisting of slight scaling erythema follicular plugs and brown pigmentation (see Figs 19 and 20) There was no telangiectasia or scarring She was afebrile mouth N A D Cardiovascular system blood pressure 106 65 N A D Respiratory system impaired percussion note and slight dullness but without adventitious sounds at the right lung base Alimentary system and genito urinary system N A D Locomotor system effusion was present in right knee joint and the right shoulder joint was painful to move

of potassium and chlorides it tends to greatly accentuate the already existing tendency to alkalosis thus producing a hypo chloraemic hypopotassaemic alkalosis This tendency is largely offset by the routine administration of potassium chloride, but should it occur further amounts of this substance should be given immediately Although the mercurial diuretic causes a marked water diuresis sodium retention is unaltered and tends to persist until ACTH or cortisone is discontinued

Mental complications

Mental complications have been discussed already but there is one feature which appears to be especially frequent in the treatment of acute disseminated lupus erythematosus and that is the high incidence of convulsions Although it is well recognized that convulsions are not infrequent in the untreated disease (Klemperer and his colleagues 1941) they have almost always represented a terminal manifestation During therapy with ACTH and cortisone however convulsive seizures are frequent and although it is difficult to ascribe this with certainty to the drugs there is some evidence that they may have at least exaggerated the latent tendency Therapy should be stopped on the appearance of convulsions but it may be possible to continue it after a few days while at the same time administering anticonvulsant drugs

A married woman aged 35 years was given sulphonamide drugs for recurrent pyelitis on four occasions during 1950 Each course of the drug evoked an urticarial eruption and soon after the last treatment the typical rash of lupus erythematosus appeared on the face neck and limbs This faded after a few weeks but subsequently systemic lesions developed arthritis of rheumatoid type renal impairment generalized lymph gland enlargement and splenomegaly Cortisone therapy was com menced in January 1951 5 600 milligrams being given in a period of 6½ weeks

This was followed by considerable improvement in the patient s general condition but after the phase of euphoria commonly seen at the onset of cortisone treatment had passed the patient became of childish and dependent mentality Her condition changed to one of depression with marked loss of confidence during a second course of cortisone in April so that despite her satisfactory physical condition she remained almost completely

Investigations showed that the erythrocyte sedimentation rate was raised to 120 millimetres per hour haemoglobin was 75 per cent white blood cells 9 000 per centimetre and the differential count normal No L E cells seen in the peripheral blood Blood urea 32 milligrams per cent albumin and acetone were present in the urine and the Esbach s quantitative test resulted in 2 grammes per litre X ray examination of the chest showed slight pleural thickening at both costophrenic angles but no other abnormality

Treatment

Treatment commenced with the administration of mepacrine 0 1 gramme daily this being increased to 0·1 gramme three times daily aspirin was also given A month later the patient developed joint swellings and tinnitus and because of these symptoms both drugs were stopped Two days later the mepacrine was restarted and the dosage gradually increased till the patient was receiving 0 2 gramme three times daily The following week the erythrocyte sedimentation rate had dropped to 58 millimetres per hour but a day after this estimation it suddenly increased to 113 millimetres per hour and the patient developed nausea and vomiting The mepacrine was reduced to 0 1 gramme thrice daily

As the general condition had not improved a week later ACTH was started The erythrocyte sedimentation rate was 115 millimetres per hour The patient was given 25 milligrams of ACTH intravenously daily for 2 weeks and then the dose was reduced by 5 milligrams daily to 5 milligrams a day and this dose was given for 3 days At the end of 1 week the erythrocyte sedimentation rate had dropped to 40 millimetres per hour ACTH was given for 21 days and then discontinued The day following the patient developed a temperature of 101 F and signs at the right base suggestive of consolidation A chest skiagram showed signs of early pneumonic consolidation Penicillin therapy was commenced The patient failed to respond to the penicillin and further ACTH was recommended She was given 20 milligrams intravenously daily for 4 days 15 milligrams intravenously for 1 day and then 15 milligrams intravenously four times daily for another 4 days ACTH was continued 10 milligrams four times daily for 1 day and 5 milligrams four times daily for 1 day By the evening of this last mentioned day the patient had developed severe pain at the back of the head and behind the eyes and the left side of her face was again swollen ACTH was increased to 10 milligrams four times daily with almost



Fig 19 —*Lupus erythematosus* beginning of treatment



Fig 20 —Lupus erythematosus (same case as in Fig 19) during treatment

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FIG 21 —Lupus erythematosus (same case as in Fig 19) after treatment Note skin lesions have disappeared but considerable wasting has occurred.

immediate improvement penicillin was discontinued ACTH which had been given in doses of 10 milligrams four times daily for previous 16 days was reduced at the rate of 1 milligram per dose per day and then later by 1 milligram per dose on alternate days to a level of 1 milligram four times daily and then discontinued Ten days previously the erythrocyte sedimentation rate was 100 millimetres per hour

The patient was discharged a week later and now at the time of writing 5 months later the patient s condition is still good and she is able to do light housework but she still has a marked lupus erythematosus rash on her face and a patchy erythema of her scalp She tried working as a machinist but found the work too exhausting She has now been found a job suited to her capabilities She developed hirsuties during treatment but the hair has subsequently fallen out (Fig 21)

This case demonstrates the increased susceptibility brought about by ACTH to infection and that if the drug is suppressive only, the fundamental process has to burn itself out

CHRONIC DISCOID LUPUS ERYTHEMATOSUS

These drugs would seem to have relatively little place in the treatment of this condition as opposed to their use in the acute and subacute disseminated forms of the disease

Most observers have noted that the drugs cause complete or moderate involution of the lesions in most cases but that there is usually a prompt relapse on cessation of therapy

It is not justifiable in the present state of our knowledge to contemplate maintaining patients with this form of the disease on continued doses of the hormones

The only case that the author has treated was severely disfigured by a lesion on the nose Carbon dioxide snow therapy had produced only moderate improvement A superadded neurodermatitis developed ACTH therapy enabled her to travel to the tropics with an almost normal face She has remained well for 5 months An example of the splinting or crutch action is mentioned by Sulzberger (1952)

PEMPHIGUS

In attempting to evaluate the treatment of this condition it is necessary to consider the different varieties of the disease separately These are pemphigus vulgaris pemphigus vegetans and pemphigus foliaceus The two latter varieties are much less common than the first

Pemphigus vulgaris

This is an almost invariably fatal disease which exists however in varying degrees of severity a fact which has led some to divide it into acute malignant and benign chronic pemphigus a false distinction In all cases this is a disease characterized by exacerbations and remissions In the fulminating forms the patient rarely survives for long although there are exceptions to this rule even in untreated patients while in the more chronic forms patients have been known to survive over 20 years All these facts are important when attempting to decide exactly what effect any given form of therapy has had on the natural course of the condition The experience of

the various authors who have so far published reports on the treatment of this disease agrees on many points but differs very considerably on others the difference even when making due allowance for varying dosages of ACTH and cortisone and variations in the severity of the disease, make an assessment of the degree of usefulness of the hormones in pemphigus a matter of some difficulty

There are some facts however, about which there is more or less general agreement

In the treatment of pemphigus vulgaris therefore the adminis tration of an adequate dose of cortisone or ACTH appears to exert certain beneficial effects in almost every case (Lever and his colleagues 1951 Kierland and Brunsting 1952, Andrews 1952 Costello 1952, Canizares 1952)

In almost every instance there was a reduction in the number of fresh bullae appearing a lowering of temperature and feeling of well being within the first 48 hours Within a week or so fresh bullae either ceased to appear altogether or were very few in number while the epithelialization of denuded skin areas appeared to proceed rather more rapidly after 7–10 days of treatment (Cannon and his colleagues 1951) This is quite compatible with the delay in wound healing noted during ACTH or cortisone therapy since these are mesodermal tissues while the epidermis is of course ectodermal

It was noted by Frazier Lever and Keuper (1951) that the mucous membrane lesions of pemphigus vulgaris although improving greatly and enabling patients to eat well who had previously been almost unable to do so did not respond as well to the drugs as the cutaneous lesions These observers also noted that their patients with the more chronic forms of pemphigus vulgaris seemed to show a less complete response than those with the fulminating type of the disease and new lesions were prone to continue to form

In the very acute forms of the disease symptomatic control of the sort described has frequently been life saving and in fact many reported cases have been moribund when treatment was begun The majority had also received most of the

usual forms of treatment including antibiotics and Germanin After the disease has been brought largely under control there have been some patients who have remained completely free from lesions for varying periods of time but the more usual experience has been that they still have occasional lesions recurring and with others healing even during a remission Sulzberger and his colleagues (1951) reported one of the most unfavourable series of cases despite the use of adequate doses of the drugs Of 5 patients 3 received only slight or moderate benefit, 1 of these having had two courses of ACTH and one of cortisone while another relapsed immediately and died 16 days later and the third was only benefited when Suramin was given in addition to the ACTH following which he cleared completely A fourth case had no benefit whatsoever

It seems hardly possible to ascribe this all to low or insufficiently sustained dosage and it is a reminder that failures will probably occur

Mr C B was admitted with pemphigus vulgaris and gave the following history He was quite well until 3½ years before admission when whilst in India he developed a warty lesion on his right temple This gradually progressed He was seen by a dermatologist in England 4 months after the onset and the condition was diagnosed as a dermatitis medicamentosa He returned to India and shortly afterwards he was awakened one night by intense irritation By next morning he had developed a widespread bullous eruption He was invalided home but by the time he reached England the bullous eruption had cleared The original lesion remained Shortly after this the bullous eruption recurred and was diagnosed as dermatitis herpetiformis Subsequently the condition remitted and relapsed twice With the second relapse he developed generalized exfoliation and was admitted to hospital where he remained for 4 months during which time he received penicillin blood transfusions and aureomycin The last mentioned was of limited benefit only Following his discharge he remained at home for 18 months His condition remained unchanged during this time While at home he was seen by several dermatologists who variously diagnosed the condition as seborrhoeic dermatitis Senear Usher syndrome and non specific exfoliative dermatitis

On examination he was found to have a generalized exfoliative dermatitis associated with generalized glandular enlargement His hair was sparse He had conjunctivitis but the oral and urethral mucosae were normal

Investigations resulted in the following Blood count haemo globin 75 per cent colour index 1 white blood cells 8 000 per cubic millimetre differential count and the plasma proteins were normal Chest x ray examination showed pleural thickening at the left costo phrenic angle Biopsy was carried out and showed an intra epidermal bulla with acantholysis of the prickle cells Previous biopsies had shown a non specific exfoliative dermatitis (Figs 22 and 23)

Treatment

Intravenous ACTH was started in a dosage of 25 milligrams daily After 7 weeks this was reduced to 20 milligrams daily intravenously Phenergan was also administered to control the itching At the end of the eighth week he developed a tenosyno vitis of his right wrist which slowly improved and a week after this a few small skin bullae appeared After 9½ weeks on ACTH he was noticed to have a moon shaped face Two days later he developed a mild pneumonia of his left lung base This responded rapidly to penicillin Nearly 3 months after starting ACTH the dose was reduced to 15 milligrams daily and 4 days later to 10 milligrams daily For the 3 previous weeks his blood pressure had been rising slowly He was found at this time to have heavy glycosuria A glucose tolerance curve was carried out and was found to be of a diabetic type Because of the above complications the ACTH was reduced to 5 milligrams daily and shortly after to 5 milligrams on alternate days It was discontinued 10 days later —nearly 4 months after commenc ing treatment

Throughout the course of ACTH there was a gradual but steady improvement in his skin condition For several days during the pneumonia it deteriorated slightly At the time of discharge it was normal in colour There were scattered areas of thickening associated with slight scaling

On the day of discharge he was started on oral cortisone 75 milligrams daily This he continued and when seen 3 months later prior to his departure overseas there were no signs of relapse His blood pressure was 155/105 and his urine was free from sugar

This case demonstrates the complications of hypertension and diabetes due to ACTH and as maintenance therapy was necessary he was changed on to cortisone just prior to discharge



FIG 22 —Pemphigus vulgaris



FIG 23 —Pemphigus vulgaris Responding to treatment and becoming more like pemphigus foliaceus

Pemphigus vegetans

This variety of pemphigus is considerably rarer than pemphigus vulgaris and in general is considered to have a better prognosis However, it is an extremely disabling disease, apart from its mortality, on account of the pain and discomfort attendant upon the discharging vegetations in the mouth and flexures

Relatively few cases have been reported following treatment with ACTH and cortisone but they have been almost universally promising the response being generally more uniform than in the case of pemphigus vulgaris Thus, in most instances bulla formation ceased within 24-48 hours while after 7 days the temperature was normal and the exuberant vegetations were flattening and were for the most part healed within 3 weeks

One very striking thing noted in most cases was the very rapid response of mucous membrane lesions the patients being able to eat comfortably within 4 days or so whereas previously they were scarcely able to do so The effects on the lesions of mucous membranes seem to be rather more pronounced than in the case of pemphigus vulgaris It should be pointed out that the cases described by Cannon and his colleagues (1951) Brodthagen Reyman and Schwartz (1951) and Newman and Feldman (1951) were almost moribund when treatment was begun and the response was almost dramatic

Pemphigus foliaceus

Again only relatively few cases of this condition have as yet been treated with ACTH and cortisone and the results have so far been very conflicting so much so in fact that one can hardly do more than summarize the existing points of view This variety of pemphigus like pemphigus vegetans bears on the whole a somewhat better prognosis than pemphigus vulgaris but it is once again a very disabling condition Kierland and Brunsting (1952) found that bullae ceased to appear and the exfoliation was greatly reduced in all their cases Moreover the effects were prolonged after cessation of therapy to a greater extent than in the case of pemphigus

vegetans an effect also noted by Lever (1951) Similar results were reported by Homburger Bonner and Fishman (1950) The cases described by Sulzberger (1952) and Farber and Walton (1952) did not respond at all however to 100 milli grams daily of ACTH while those of Frazier Lever and Keuper (1951) while responding did not improve as rapidly *and the duration of remissions was less prolonged than in the* case of pemphigus vegetans although the doses of the drugs used by these latter authors were relatively high—from 200 to 300 milligrams of ACTH daily or 300–500 milligrams of cortisone

Dosage in pemphigus treatment

As might be expected there is no agreement as to the most effective general scheme of dosage for treating this group of disease

It would seem to be agreed however that it is essential to start with relatively high doses of the drugs the exact dose varying of course in each individual If symptomatic control is not achieved in a short time the dose must be increased until it is secured initial dosage seems to be particularly necessary in the case of pemphigus since many observers have noted that successive relapses may necessitate higher and higher doses of the drugs if during each course the disease is not brought properly under control For this reason Lever and his colleagues (1951) advocate that the initial high dosage *should be continued for 3–5 weeks at least or until a complete* remission is obtained Then the drug is discontinued com pletely until the disease relapses when a further adequate course of treatment is given This method is also advocated by Frazier Lever and Keuper (1951) They suggest 200–300 milligrams of ACTH or 300–500 milligrams of cortisone daily On the other hand Kierland and Brunsting (1952) considered that the best results were obtained by a constant maintenance dose following the initiation of a remission This method is also favoured by Sulzberger and Baehr (1951) who also note that as the remission continues the dose of the drug needed to maintain it often get steadily less One should

remember, however, that if the maintenance dose is a high one undesirable effects may appear (Teicher and Nelson 1952)

Although they are much less frequent serious complications of the sort seen during the treatment of acute disseminated lupus erythematosus may sometimes occur

A variety of pemphigus so called which affects the mucous membranes mainly of the eyes, mouth upper respiratory and digestive tracts and even the vagina has been described It may or may not be a true variety of pemphigus but leads to extensive scarring of the areas involved and even strictures Bullae do not appear on the skin except sometimes round the edges of the mouth

In 2 cases treated by Frazier Lever and Keuper (1951) the activity was arrested and bullae ceased to appear but scar tissue was of course unchanged

DERMATOMYOSITIS

This condition is one which varies very considerably in its severity It can exist as a fulminating febrile disease with a high mortality a subacute type or a relatively chronic form in which the course is extremely lengthy and also the death rate is low The acute form of the disease usually but not always progresses to a fatal termination in from a few weeks to a few months while in the subacute and chronic forms of the disea e death may sometimes supervene after many years and probably about 50 per cent of all patients affected ultimately die It is difficult therefore to accurately evaluate the effects of ACTH and cortisone on its course but most reports indicate that they have not been as useful as they have in acute disseminated lupus erythematosus or pemphigus

The evidence in general suggests that if the disease is treated very early and with large doses of the drugs moderately good results may be obtained (Ferguson Rosenbaum and Tolman 1952) In many of the reported cases the disease had been present for periods of time exceeding 1 year and in most of these the results were uniformly disappointing

This is fully in accordance with our knowledge that cortisone merely shields the tissues from damaging effects of disease and its action is likely to be most dramatic therefore when the effects are maximal that is in the acute stages of the condition O Leary (1951) was however unable to influence a case in any way during the acute phase although some slight improve ment occurred in the chronic stage This may, however have been due to rather low dosage Lever and his colleagues (1951) treated 8 children and 3 adults with acute or subacute forms of dermatomyositis with fully adequate doses of the drugs but despite this 3 children and 1 adult died while in 4 children and 1 adult the disease entered a partial remission and in the remaining 2 cases the remission was complete When evaluating these rather poor results one must remember that the disease in any case has quite a strong tendency to spontaneous improvement

This experience is fairly typical however In a successful case the oedema subsides the temperature falls to normal the rash gradually disappears the skin softens and there may be also some increase in muscle strength (Thorn and his colleagues 1950)

In view of the serious nature of the disease the dosage of the drugs should be similar to that recommended in the treat ment of pemphigus and acute disseminated lupus erythema tosus the initial doses of cortisone being in the region of 200-500 milligrams daily and of ACTH 100-300 milligrams daily by intramuscular injection The dose should then be adjusted according to the clinical response and severity of the disease and raised or lowered accordingly

An extremely careful watch should be kept on the nitrogen balance in view of the fact that there is already in this condition considerable breakdown of muscle protein If and when a remission is induced the dose of the drug should be gradually reduced and finally discontinued In cases which show a response it is not possible in the light of the available evidence to say whether the best results are to be obtained by a continuous maintenance dose or intermittent therapy

EXFOLIATIVE DERMATITIS

This condition may be idiopathic or may occur during the course of other skin diseases such as dermatitis and eczema psoriasis lichen planus seborrhoeic dermatitis and pityriasis rubra pilaris It may also follow the systemic administration of drugs such as arsenic and gold or result from allergic sensitization to topical applications

The type which occurs during the course of lympho blastomatosis will not be considered here

In this incapacitating and often fatal disease ACTH and cortisone are the treatment of choice

In those cases in which the condition has been caused by drugs the results have been uniformly successful the scaling erythema and pruritus being vastly improved within 7 days while the eruption has completely cleared in a further 2–3 weeks and provided the causal agent has been removed relapse has usually not occurred

In 1 case reported by Steiner and Frank (1952) the unsuccess ful result was probably due to insufficient dosage

In cases due to causes other than drugs the response has been *in most cases equally encouraging but as one might* expect there has been a tendency to relapse after treatment is stopped Two idiopathic cases reported by Lever (1951) had some considerable degree of remission for many months after treatment was stopped

Those cases due to psoriasis will be considered under that heading

In view of the seriousness and incapacitating nature of this disease *the dosage of ACTH or cortisone must be adequate* and the initial dose should probably not be less than 300 milligrams of cortisone or 150–200 milligrams of ACTH daily This can then be reduced a little after a few days but should be kept at a fairly high level—200 milligrams cortisone—until the condition is fully controlled *The dose may then be reduced until it can be discontinued completely* as in the case of those due to drugs or a suitable maintenance dose found and

continued In the event of failure to respond to either drug the dosage should be increased until a response is obtained

Complications have been relatively few but mental disorders and circulatory failure have been reported All the usual precautions and investigations should accompany treatment

SCLERODERMA

Diffuse scleroderma and so called acrosclerosis as opposed to the localized form or morphoea will be discussed here The diffuse form of the disease is usually progressive often ending fatally usually from intercurrent disease after a varying period of time which may be many years

Acrosclerosis on the other hand tends to have a better prognosis and frequently burns itself out in the course of time

It is important to bear in mind the essentially chronic nature of most cases of the disease since this has to be taken into account when considering maintenance therapy

Most observers have reported improvement in diffuse scleroderma of a varying degree following ACTH or cortisone treatment This improvement has taken the form of softening with increase in mobility of the skin and diminution in pain soreness and discomfort resulting in considerably increased ability to perform many simple tasks which were previously impossible Pain and stiffness in joints were also reduced The softening of the skin relieved dysphagia and also restriction of respiratory movements *(Kierland and Hines 1951)* These changes were not limited to cases in which the disease was of relatively short duration although under these circumstances the response was maximal but were also seen in patients who had had the disease for as long as 10 years (Berry 1952) On the other hand there are some instances where patients have received adequate doses of the drugs without any obvious benefit (Ferguson Rosenbaum and Tolman 1952 Brodthagen Reyman and Schwartz 1951)

As soon as treatment was discontinued however the disease tended to relapse in some cases remissions lasted for some months

Maintenance therapy prevents relapses but if one is going to consider it presumably one has to face the prospect of continuing it indefinitely It is not possible as yet to say whether the risks to the patient and the best chance of relieving his symptoms to some extent will lie in intermittent courses of the drugs or a constant maintenance dose A better clinical response tends to favour the latter while against it is the risk of complications Only when much more experience has been gained will these questions be answered In any case in a disease which may be progressively disabling and ultimately fatal continued administration of ACTH and cortisone would seem at least to be justified if the clinical response merits it

A patient treated by Sharnoff and his colleagues (1951) who despite improvement subjectively developed an irreversible hypertension and died in uraemia sounds a note of caution for while renal lesions are well known in diffuse scleroderma the possibility exists that the hormones may have exaggerated pre existing damage In any case it is known that ACTH and cortisone do not affect the underlying disease process and in view of its known visceral and particularly renal effects very careful watch should be kept on the blood pressure and renal function of cases receiving the drugs

The response of cases of acrosclerosis has been rather more variable In some instances the cutaneous sclerosis decreased and pain and joint stiffness disappeared with a considerable increase in functional ability while in others the condition was materially unchanged despite adequate doses of the drugs

It would seem therefore that a trial of cortisone or ACTH is only indicated in this type of scleroderma if the disease is at all crippling The same problem as is mentioned under diffuse scleroderma exists in relation to interrupted courses or continued maintenance therapy when an initial improvement has been gained

ERYTHEMA MULTIFORME

The severe form of bullous erythema multiforme known as the Stevens Johnson syndrome appears to be benefited by ACTH

and cortisone Since it is a self limited disease some caution is necessary in assessing the results However the dramatic improvement which can occur in 36–48 hours in a disease which may cause blindness suggests that ACTH and cortisone may reasonably be given The present lack of evidence makes it impossible to say much more especially as the coincident secondary infection so often present indicates the use of antibiotics with the hormones and thus further complicates the issue

DERMATITIS HERPETIFORMIS

So few cases of this condition have been treated that it is only possible to say that the reports are hopelessly conflicting

In any case the use of these drugs in such a condition could only be considered when all the standard forms of treatment had failed

This writer is at present treating with ACTH a woman aged 49 years who is suffering from dermatitis herpetiformis This patient who at first presented a typical picture of sub acute dermatitis herpetiformis, subsequently developed very many large bullae all over the skin surface except for the scalp she also had them on the oral mucosa ACTH 25 milligrams intra muscularly 6 hourly was given for 5 days and then increased to 50 milligrams 6 hourly but was reduced to the former level after 2 days because of the development of hypertension facial rounding and increase in weight of 14 pounds

Lesions in her mouth which had appeared last were also the slowest to resolve On the suggestion of Professor Pickering cortisone was applied locally to these lesions in the form of a paint This appeared to accelerate recovery

After 19 days on the drug her skin was clear apart from an odd vesicle

LYMPHOBLASTOMA

ACTH and cortisone have been administered to patients with acute and chronic leukaemias Hodgkin s disease and mycosis fungoides

The results of treatment in all these conditions may be summarized by saying that they all show some response but that the process recurs when the drugs are discontinued Moreover response to further treatment in many cases then seems to be less satisfactory or even entirely absent a feature which is regularly observed in the treatment of this group of diseases by other methods

One of the most constantly observed effects of the drugs in these conditions has been the relief of the intractable pruritus which is often present and which is not infrequently unrelieved by x ray therapy or nitrogen mustard This would seem to be an absolute indication for the administration of ACTH or cortisone and in some cases the symptomatic improvement has been maintained for some months

In a case of mycosis fungoides with generalized erythroderma 100 milligrams of cortisone daily for 72 days resulted in great improvement Without maintenance therapy however the condition relapsed in 3 weeks

PERIARTERITIS NODOSA

This is a comparatively rare disorder characterized by necrosis hyalinization of the media of small vessels accompanied by a perivascular infiltration of mononuclear polymorphonuclear and eosinophil cells After partial recovery fibrosis of the adventitia leads to nodules This disorder may be limited to the vessels of one system

The clinical picture is varied There may be non specific or chronic pyrexial illness an atypical abdominal illness *primary renal disease or combination of polyneuritis* and polymyositic features

The cases are *usually seen by dermatologists on account of* scarlatiniform eruptions urticaria vesicular and bullous eruptions *The bullae are often haemorrhagic* and may ulcerate leaving a shining depressed scar (Cecil and Loeb 1952)

The disease is probably a *hypersensitivity reaction to a* varied group of substances including bacterial toxin sulphon amide and thiouracil

The prognosis is poor with a few remissions and only rare recoveries

In this disorder ACTH has a valuable place in therapy although the course may continue and the supply and dose of the drug become a doctor s dilemma

Mr J A aged 52 years was admitted to hospital with periarteritis nodosa and gave the following history

Three years previously the patient had noticed the onset of pains in the muscles of the backs of the thighs These were worse when he was tired but were not appreciably affected by movement or weather Despite the pains he was still able to work Shortly afterwards he developed painful swellings of the right ankle joint which varied from time to time despite symptomatic treatment About this time he noticed small red areas on his skin which enlarged to about 3 millimetres in diameter These then became scaly and on some crusts developed which fell off leaving ulcers which healed slowly There also developed a red mottling of the skin which started on the lower legs and gradually extended upwards to involve the trunk and forearms During the next 6 months his knee joints became swollen and painful He had various treatments including a course of gold without effect He then developed swelling stiffness and pain in his wrists and finger and elbow joints and had severe pain unassociated with his joints in his limbs Just over a year after the onset of symptoms he noticed nodules on his skin especially over the dorsum of his forearms These were tender never larger than a grain of wheat and some disappeared spontaneously About this time he began to suffer from severe lassitude to tire easily lose weight and to suffer from sweats Sometime later while playing golf he suddenly developed a fullness and heaviness in his right arm which became stiff and swollen and remained so for 6 weeks He gave no past history of disease apart from some eye trouble 7 years previously which had been treated with sulphonamides

On examination there were several small firm subcutaneous nodules on the extensor surfaces of the forearms There were purple reticular markings forming irregular patches on the arms and legs Pigmented scars were present on his arms and legs at the sites of previous ulcers There were punched out ulcers on both buttocks and on the right toe His nails were dystrophic The joints were normal apart from some periarticular thickening Examination of the cardiovascular system revealed signs of a right subclavian venous block dilated veins were present in the right arm right neck and running across the

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PERIARTERITIS NODOSA

This is a comparatively rare disorder characterized by necrosis hyalinization of the media of small vessels accompanied by a perivascular infiltration of mononuclear polymorphonuclear and eosinophil cells After partial recovery fibrosis of the adventitia leads to nodules This disorder may be limited to the vessels of one system

The clinical picture is varied There may be non specific or chronic pyrexial illness an atypical abdominal illness primary renal disease or combination of polyneuritis and polymyositic features

The cases are usually seen by dermatologists on account of scarlatiniform eruptions urticaria vesicular and bullous eruptions The bullae are often haemorrhagic and may ulcerate leaving a shining depressed scar (Cecil and Loeb 1952)

The disease is probably a hypersensitivity reaction to a varied group of substances including bacterial toxin sulphon amide and thiouracil



Fig 24 —Periarteritis nodosa



Fig 25 —Periarteritis nodosa

right side of the chest His blood pressure reading was 105/65 (*see* Figs 24 and 25)

Biopsy of a subcutaneous nodule was reported as a good example of periarteritis nodosa acuta A blood count showed his haemoglobin to be 75 per cent red blood cells 3 800 000 per centimetre white blood cells 1 500 per centimetre Urinary investigations were normal and so were chest skiagrams and a barium swallow and skiagrams of the hand wrist elbow and knee joints His erythrocyte sedimentation rate was 75 millimetres per hour

Treatment

ACTH intramuscularly 100 milligrams daily was started and within 4 days the limb and joint pains had disappeared By the second week there was no sign of the joint swellings and by the third week the buttock and toe ulcers had healed The erythrocyte sedimentation rate fell steadily and was normal by the fourth week After 3 weeks the dose was gradually reduced so that he was receiving 50 milligrams daily by the fifth week When on this amount he developed fresh nodules on his forearms He was then changed over to cortisone 100 milligrams daily which he administered himself He was discharged on this regime

He continued on the above regime as an out patient He was able to work and to play golf After 4 weeks the dose of cortisone was gradually reduced Three months after discharge he was on 50 milligrams a day Four months after discharge he was taking only 31 milligrams a day but he developed red reticular patches on the forearms and joint swellings whereupon the dose of cortisone was increased to 50 milligrams a day and continued at that level for another 2 months He was then given 50 milligrams of cortisone orally daily which was then gradually reduced but when a level of 20 milligrams a day was reached symptoms again appeared so the dose was again increased to 50 milligrams

He was readmitted some 3 months after discharge with a further flare up of his periarteritis nodosa which was again controlled by parenteral cortisone He continues to remain well on 100 milligrams a day which he is taking as an out patient The disease is still active but its manifestations can be suppressed with cortisone

In this case the disease although still active is controlled with cortisone so that he is able to lead a useful and active life It is hoped that in time the disease process may heal spontaneously

ALLERGY AND HYPERSENSITIVITY

It is now generally conceded that apart from the treatment of severe and fatal diseases one of the main indications of the use of cortisone is to suppress the symptoms and reduce the morbidity of self limited conditions such as drug eruptions and contact dermatitis when the offending allergen has been removed

In other more chronic diseases such as long standing atopic eczema the use of the drugs is regarded as being justified to assist the patient through a severe phase of the condition although their continuous use in such conditions is not as yet generally recognized or practicable

The often dramatic effects of ACTH and cortisone in reducing the symptoms of allergic hypersensitivity reactions are not thought to be due to their preventing any phase of the reaction between antigen and antibody but to some effect which presumably acts at tissue levels thus preventing in some way the usual ill-effects of antigen and antibody union in the sensitized cells However nothing is known of the exact mechanisms involved and the whole state of affairs becomes more than ever confused by experimental results such as those of Sulzberger Witten and Zimmerman (1952) which demonstrated that positive patch tests could be obtained in sensitized subjects while cortisone was being administered The very slight diminution in the extent of the reaction was in no way sufficient to account for the therapeutic effect in sensitization dermatoses Thus the anomalous situation exists whereby positive patch test reactions may presumably be produced in a patient whose skin manifestations of the allergic reaction are simultaneously being suppressed by the hormones Other authors however found that cutaneous sensitivity is diminished during cortisone therapy (Hopkins and his colleagues 1952)

Contact dermatitis

In view of the dramatic effects of ACTH and cortisone in diminishing the inflammatory reaction resulting from dermatitis venenata and thus preventing or minimizing the effects of

MISCELLANEOUS DERMATOSES

Extensive lichen planus with intractable pruritus which had been unaffected by treatment with intramuscular bismuth and x ray therapy was treated in 2 cases by Kennedy and his colleagues (1952) Cortisone was given in doses of 100 milligrams daily for 5 days and then 100 milligrams on alternate days for a further 6 injections The response in each case was dramatic symptoms being immediately relieved while there were no side effects or withdrawal symptoms When seen 6 weeks later only a few pigmented areas were visible Hopkins and his colleagues (1952) reported a case in which the symptoms improved in 48 hours and the lesions had cleared in 15 days Four months later there was a return of the condition It is not possible in a disease such as lichen planus to draw any conclusions from these reports other than that they are suggestive

In 3 reported cases of Kaposi s idiopathic haemorrhagic sarcoma there was a complete lack of response to the drugs

The treatment of alopecia totalis in 2 patients was a total failure

In 2 cases of epidermolysis bullosa no therapeutic effects were noted (Cannon and his colleagues 1951)

TOPICAL THERAPY

Local applications of cortisone varying in strength from 5 to 25 milligrams per gramme of ointment base have been uniformly unsuccessful in the hands of most observers except perhaps in the treatment of lesions of the eyelids In this region the instillation of drops into the eye may allay contact dermatitis and neurodermatitis of the eyelids

An exception to this general experience was a report by Newman and Feldman (1951) in which they produced some effect on lesions of chronic discoid lupus erythematosus and more particularly in 2 cases of necrobiosis lipoidica diabeticorum The preparation ultimately used was 25 milligrams of cortisone in a Carbowax base

Drug eruptions

These reactions which consist of urticarial morbilliform scarlatiniform erythema multiforme like eczematous exfoliative and other types should only be treated with ACTH and cortisone when normal methods of therapy have failed and the condition is of distressing severity

The type of eruption which has been treated most frequently with the hormones is the serum sickness type of reaction with urticaria which not infrequently follows parenteral penicillin This condition may sometimes last for many weeks if untreated and if it fails to respond to antihistamine drugs ACTH or cortisone will produce a dramatic effect Within 24 hours patients covered with giant urticaria and suffering from arthralgia and intolerable itching have been restored almost to normal

In most cases the drug of choice as in contact dermatitis would seem to be oral cortisone in an initial dose of 200 milligrams followed by 100 milligrams daily for 5–7 days depending upon whether there are any signs of recurrence when the drug is withdrawn Should such signs occur a small maintenance dose of 50 milligrams or so should be maintained until this tendency has subsided

In all drug eruptions as in the case of contact dermatitis it is essential before treating with ACTH or cortisone to be certain that the causal allergen has been removed

The other types of drug eruptions mentioned are less likely to require hormone treatment since in many of them the subjective symptoms are not so severe In those cases where treatment is considered necessary however the results are almost equally favourable although treatment may have to be continued for a little longer In any case the dose schedule should be as recommended for the serum sickness reactions and varied as necessary according to the individual response It is essential to emphasize here that the use of ACTH or cortisone in no way supplants the need for adequate local therapy but should be regarded as an adjunct to it Such remedies should be all the more effective since the

scratching secondary infection and bacterial or auto sensitization with spread of the eruption their use in these conditions is fully justified provided that the offending allergen has been removed and that there are no general contra indications to their use particularly as the amounts of the drugs needed to treat these conditions is extremely small and the chance of side effects therefore negligible

Where any degree of secondary infection is present local or systemic antibiotic therapy should be administered as indicated

Immediately following the start of therapy with cortisone or ACTH there is relief of itching within 12 hours and a subsidence of the oedema and exudation within 24 hours while in some cases within 2–3 days the skin may be almost normal This very rapid response is seen in recent cases (Falk Allende and Bennett 1952) but cases of longer standing although responding completely to the drugs may take longer to do so (Hopkins and his colleagues 1952) and require a greater total dosage

Kesten (1952) has said that while on cortisone 5 patients were rapidly desensitized to the chemicals causing their derma titis

The most satisfactory dosage schedule would seem to be similar to that suggested by Dorph and Katzenstein (1952) and the most convenient drug to use is oral cortisone An initial dose of 200 milligrams followed by 100 milligrams daily for a total of 5 days is sufficient in most cases When the course is so short further experience may indicate that many of the normal laboratory procedures may be dispensed with and out patient treatment may even be possible

It should be explained that until such experience is forth coming however these cases should have all the recommended investigations carried out and the treatment should only be given in hospital

It is useful to recall that short courses do not lead to depression of the adrenal cortex and the drugs may be discontinued abruptly without fear of withdrawal symptoms developing

universal occasional reports have described periods of remission or partial remission lasting some months (Kennedy and his colleagues 1952 Farber and Walton 1952)

In addition to the prompt and often serious relapse on cessation of therapy due partly to post cortisone or post ACTH adrenal or pituitary depression a severe depressive mental reaction may be encountered coincident with the relapse for patients with long standing atopic eczema are necessarily to some extent adjusted to their condition and when a drug capable of relieving it is exhibited to them and then withdrawn the mental effects are severe often resulting in a condition worse than the original one

Maintenance doses have been given in an attempt to prevent this state of affairs and in every instance this is successful provided an adequate dose is given

Thus Ferguson Rosenbaum and Tolman (1952) found it necessary to give 100–200 milligrams of cortisone daily to prevent relapse and the experience of Sternberg and his colleagues (1952) was similar On the other hand Hopkins and his colleagues (1952) and Sulzberger (1952) have been able to maintain remissions on doses as small as 25–50 milligrams of cortisone daily

At the present stage of the experience with these drugs it is generally agreed that it is not justifiable to maintain these patients on maintenance doses unless the circumstances are exceptional since the condition is so chronic and in view of some of the dangerous ill effects of continued dosage with the hormones Further experience may indicate that if the daily maintenance dose is small enough it may be quite safe but this cannot yet be assumed to be so

To summarize therefore treatment with cortisone or ACTH should be reserved for the more severe cases of this disease and then used preferably to assist the patient through an exacerbation In the milder forms of the condition the drugs should not as yet be used at all

The dosage of the drugs required to produce a complete remission is higher than in the case of contact and drug

patient will be unworried and the lesions dry and non irritating thus avoiding all the difficulties created by itching scratching weeping and crusting which so often make local therapy difficult

Exfoliative dermatitis whether due to drugs or not is considered in a separate section (*see* page 188)

It is interesting to note that in fixed drug eruptions and the pustular vegetating or acneiform eruptions which are caused by halogens ACTH and cortisone appear to be ineffective

Carey and his colleagues (1950) have attempted desensitization under an umbrella of cortisone or ACTH in a case where a patient became sensitive to a vitally needed drug

These drugs have also been used in the treatment of urticaria —apart from that resulting from drugs—although there would seem to be little justification for their use in such conditions especially if the disease is chronic

It is possible that they may have a place in the treatment of acute phases of angioneurotic oedema where there is any danger of involvement of the tongue or glottis

Atopic eczema and neurodermatitis

These conditions are considered together since many authorities consider them to be closely related There is also some evidence that allergic mechanisms may play a part in the production of atopic eczema although their share has been greatly over estimated by some notably workers in the United States of America

A large number of cases of these conditions have now been treated and the response is uniform and rapid Within 1 to 4 days of commencing treatment the intolerable itching has subsided the patients sleep well and the eczematous lesions begin to subside With continued therapy this progress continues until in some cases the eruption has completely cleared while in others it is vastly improved

When the dosage is adequate complete healing occurs in almost every case (Sternberg and his colleagues 1952) Unfortunately when the drugs are discontinued immediate relapse almost always occurs and while this experience has been

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which does not include considerable numbers and also adequate controls is utterly worthless except from the negative point of view Practically all the reports to date fall into this category and the only conclusion that it is possible to draw from them is that ACTH and cortisone are almost invariably useless in the treatment of psoriasis vulgaris a view endorsed by Sulzberger and Baer (1951) who also pointed out that they had observed cases to worsen during ACTH and cortisone treatment while Cohen and Distelheim (1951) reported a case of generalized erythroderma arising in a patient with psoriasis during ACTH therapy These facts may be due to coincidence but are somewhat suggestive and cannot by any means be ignored In any case particularly with these warnings in mind in an essentially chronic and relatively harmless disease such as this the use of these hormones is not only unprofitable but undesirable

Psoriatic erythroderma and arthritis

As opposed to this however is the experience of Sulzberger and his colleagues (1951) who treated 3 cases of psoriatic erythroderma with arthritis with uniformly beneficial results Both the erythroderma and the arthritis in these cases were greatly improved Other observers have had similarly good results although Ereaux (1952) has said in cases of psoriatic arthritis hormonal therapy has brought about relief of articular symptoms with a lesser improvement of the skin lesions but O Leary (1951) in the 4 cases he reports found a recurrence of both symptoms on cessation of treatment Two cases of psoriasis arthropathica reported by Steiner and Frank (1952) were unaffected although the dose of cortisone given was so small as to probably account for this

Other authors have reported failure to influence exfoliative psoriasis and arthropathic psoriasis with ACTH or cortisone but bearing in mind that even this type of psoriasis may undergo spontaneous regression it is felt that these types of the disease are definitely benefited by hormone therapy which probably represents the treatment of choice

eruptions Cortisone 300 milligrams for the first 24 hours 200 milligrams for the next day and then a continuance of the dose of 200 milligrams or a reduction to 100 milligrams if permissible appears to give the best results ACTH in doses of 100–150 milligrams intramuscularly daily may also be used If the drugs are used for more than 7–10 days they should be gradually tailed off rather than ceased abruptly as described in the section on dosage (*see* page 160)

Brunsting has stated (personal communication) Recently we have been finding ACTH to be quite effective in controlling symptoms of intolerable itching in patients with widespread eczema or exfoliative dermatitis the material being used occasionally say once or twice a week, as follows The patient is in the hospital and 10–20 milligrams of ACTH—incorporated in 500 millilitres of 5 per cent Dextrose solution in water (not saline)—is given by slow infusion intravenously, over a period of about 8 hours This procedure brings about symptomatic relief which may last 48 hours When ACTH is used in this way the patient obtains relief and the doctors are not under continual pressure to apply a variety of medicaments to the skin which may only aggravate the sensitive state

As soon as the opportunity arises it is the author s intention to try this procedure in chronic eczematous otitis externa

Infants and children

In infants and children the above limitation should also apply except that probably maintenance therapy should never even be considered in view of the known effects of the hormones on osteoblastic activity and chondrogenesis and the drugs should be avoided even in the acute stages of the disease whenever possible

PSORIASIS

In such a disease as this where spontaneous exacerbations and remissions are the rule and where hospitalization alone almost invariably produces improvement any series of cases

which does not include considerable numbers and also adequate controls is utterly worthless except from the negative point of view Practically all the reports to date fall into this category and the only conclusion that it is possible to draw from them is that ACTH and cortisone are almost invariably useless in the treatment of psoriasis vulgaris a view endorsed by Sulzberger and Baer (1951) who also pointed out that they had observed cases to worsen during ACTH and cortisone treatment while Cohen and Distelheim (1951) reported a case of generalized erythroderma arising in a patient with psoriasis during ACTH therapy These facts may be due to coincidence but are somewhat suggestive and cannot by any means be ignored In any case particularly with these warnings in mind in an essentially chronic and relatively harmless disease such as this the use of these hormones is not only unprofitable but undesirable

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When the condition has been brought under control and the signs and symptoms show no further improvement a maintenance dose of the drugs is necessary to prevent relapse The initial doses should be similar to those suggested in exfoliative dermatitis

Mr A G aged 46 years admitted with psoriasis and polyarthritis gave the following history

The psoriasis began when he was 17 years of age and was confined to the scalp where it remained for the next 15 years when the knees and elbows became affected Attacks were intermittent until 5 years before admission to hospital when he developed widespread lesions on the limbs and trunk and 1 month later arthritis of the right hand Since that time the arthritis spread to involve both hands elbows shoulders and knees and never fully remitted the psoriasis likewise had not remitted for the previous 4 years though it varied in extent and severity The patient had had various treatments including dietary regimes local applications gold and T A B injections The condition had further extended 2 months before admission

On examination there was almost complete involvement of the skin surface with psoriasis Islands of normal skin were present on the legs The face and upper chest were unaffected apart from lesions over the sternum and scattered nummular lesions on the back of the neck Exudation with subsequent crusting were present in places On the backs of the hands there were ostraceous psoriasis patches (*see* Figs 26 and 27) Active arthritis with joint effusions was present in the knee joints and active arthritis of the finger and wrist joints on both sides Gross fixed deformity of the right wrist joint was present His blood pressure was 115 70 and investigation of his blood showed his erythrocyte sedimentation rate to be 35 millimetres per hour Haemoglobin was 75 per cent red blood cells 3 800 000 per cubic millimetre and white blood cells 9 000 per cubic millimetre X ray examination of the hands showed marked arthritic changes with cartilage loss

Treatment

In view of reports from Madrid of the ACTH like effect of nitrogen mustard it was decided to try this drug Four milligrams of nitrogen mustard were given on alternate days on three occasions starting shortly after his admission Following these the patient developed an exfoliative dermatitis The affected joints were not improved



Fig 26 —Psoriasis arthropathica



Fig 27 —Psoriasis arthropathica

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FIG 28—Sarcoidosis



FIG 29—Sarcoidosis

ACTH was started 80 milligrams daily being given for the first 12 days after which the dose was gradually reduced The course lasted 29 days and a total of 1 580 milligrams was given The joint pains were relieved and the joint effusions disappeared by the third day No alteration occurred in the skin until the tenth day of the course when healing started gradually causing extensive islands of clear skin to appear in the inflamed skin The skin inflammation started again within 2 days of stopping the ACTH and was as severe as before the start of treatment within 10 days The articular symptoms returned within 3 days of the cessation of the ACTH On the thirteenth day of the treatment the patient developed an extensive pneumonia in the left lung *Staphylococcus aureus* was grown from both the blood and sputum The pneumonia was controlled following the administration of penicillin and chloramphenicol The episode barely disturbed the patient who complained of no more than a cold in the head He was ambulant within 3 days The pneumonia resolved uneventfully

Thirteen days after the cessation of the first course a second one was commenced ACTH 50 milligrams daily for 11 days was given On the seventh day of the course there was a sudden gain in weight of 8 pounds together with the development of gross oedema The urinary output became considerably reduced and albuminuria developed The skin condition was quite unchanged by this course of ACTH but there was some remission of the joint symptoms The eosinophils fell to near 0 and remained depressed for 7 days after stopping treatment Because of the fluid retention and the absence of response the ACTH was dis continued The albuminuria continued The patient died suddenly 9 days after the termination of the course

At post mortem examination the heart was found to be pale and flabby The lungs were grossly oedematous with some ante mortem thrombi The gut showed amyloid change and the spleen focal amyloidosis The kidneys showed no gross evidence of amyloid The synovial membrane of the right knee was greatly thickened and oedematous and showed reddened patches

This case demonstrates the increased susceptibility to infec tion and that fluid retention can be a serious problem

SARCOIDOSIS

Reports of the treatment of cases of sarcoidosis (Figs 28 and 29) are relatively few and have dealt with severe and generalized forms of the disease

the periphery and moderate lymph gland enlargement on either side Biopsy of the skin showed appearances which were consistent with sarcoidosis

Treatment

Left salpingectomy was performed No evidence of sarcoidosis was found in the specimen The patient was discharged Eight months later she was readmitted there was no change in her skin condition or in the appearance of the chest radiograph

She was treated with ACTH 20 milligrams daily intravenously for 19 days At the end of the course the papular lesions were less indurated but no significant change had occurred in the appearance of the chest skiagrams

When she was seen 3 months later the rash had returned to the same degree as when she was first seen

This case demonstrates the partial suppressive effect that ACTH may have The fundamental disease process was unaltered so that withdrawal of ACTH was followed by relapse

SUMMARY

In summing up the present position one may say that these drugs represent a great boon to mankind Not a panacea or cure all

As Brunsting (personal communication) has said These hormones have now been available for a sufficient time so that the indications for their use have crystallized I have recently summarized the subject as follows The chief indications for the use of cortisone and ACTH in dermatology seem to be in the control of symptoms in the case of systemic lupus erythematosus psoriatic arthritis or pemphigus vulgaris also in reactions of sensitization purpura and some exfoliative states The indiscriminate use of cortisone or ACTH in the control of chronic eczema often leads to a web of complications incidental to the dependence of the patient on the hormones and untoward symptoms result from the precipitate withdrawal of these agents

Ereaux (1952) has said that in broad terms the more recent the onset and the more acute the disease process the greater the response to ACTH and cortisone therapy Conversely

Although the tendency to spontaneous remission in this disease is well known in most of the reported cases the improvement recorded has been so abrupt as to be hardly coincidental In addition to ophthalmic pulmonary salivary gland and lymph node lesions improving considerably cutaneous lesions have also been stated to show marked involution in some cases (Randolph and Rollins 1951 Sones and his colleagues 1951)

In a case reported by Sulzberger and his colleagues (1951) there was moderate involution of the skin lesions after 11 days of therapy with 100 milligrams daily of ACTH but in 2 other patients the effects were not demonstrable

The paucity of available evidence makes it impossible as yet to say more than that ACTH and cortisone appear to have some effect upon the disease but the permanence of these changes and their full extent are as yet uncertain In view of some evidence of impaired adrenal function it would seem preferable to use cortisone rather than ACTH in this condition

Miss E S aged 29 years was admitted with sarcoidosis and gave the following history

In September 1950 she developed anorexia shortness of breath on exertion and lassitude On March 6 of the following year she awoke one morning to find a non itching rash on her arms and left leg There was no history of drug ingestion apart from an occasional aspirin She had lost 2 stone in weight since the onset of symptoms There was no relevant family history and her own past history consisted of a right salpingectomy 3 years previously

On examination she was seen to be a pale young woman There was a moderately profuse brownish maculo papular rash on the extensor and flexor surfaces of the forearms and lower part of the upper arms and on the legs and a few on her back The lesions varied in size from that of a pin s head to that of a grain of wheat some were grouped in small patches There were a few shotty glands in the groins

Investigation of blood showed the following results erythrocyte sedimentation rate 6 millimetres per hour haemoglobin 95 millimetres per cent white blood cells 3 600 per cubic millimetre polymorphs 43 per cent lymphocytes 49 per cent monocytes 6 per cent and basophils 2 per cent Sputum examination was normal Chest x ray examination showed bilateral diffuse mottling in both hemithoraces tending to diminish towards

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the more chronic the disease the less likely is it for restitution to integrity to occur when these hormones are used

This modern discovery may be invaluable to the right patient given under the careful control of a team consisting of a general practitioner, a biochemist and a dermatologist

G B MITCHELL HEGGS

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CHAPTER 6

DISEASES OF THE HAEMOPOIETIC SYSTEM

INTRODUCTION

BOTH ACTH and cortisone have remarkable effects on the haemopoietic system and directly or indirectly on the cells of the circulating blood Thus it is well known that in a normal human being injection of a small quantity (25 milligrams) of *ACTH is followed by a considerable drop in the* circulating eosinophils which reaches a maximum within 4–6 hours This effect is observed so constantly that it has been suggested as the basis of a test of adrenal function (Thorn and his colleagues 1948)

In addition to the effects on the eosinophils the other leucocytes are also affected The polymorphonuclear neutrophils appear in large numbers and the lymphocytes may decrease but this latter is a very inconstant finding in man and usually there is no change This contrasts strongly with the finding in animals (Dougherty and White 1944)

The effect on the blood platelets is not so marked but a moderate increase is the rule

These findings all relate to those observed in normal healthy volunteers In patients suffering from various disorders of the blood in addition to the findings enumerated above others may be noted—for example a reticulocytosis and an increase in the red cell count in some cases of anaemia

A considerable volume of work has been done in the last 3 years by way of research into many and varied haematological conditions In some cases remarkable success has been achieved—success which has often only been temporary—while in others no beneficial results have been achieved It is the aim of the author to review briefly this work and the

results and to indicate those conditions in which the use of these expensive and powerful hormonal drugs might be justified in the light of present knowledge

THE LEUKAEMIAS

The aetiology of acute leukaemia is still unknown In fowls the disease can be transmitted by cell free filtrates and is apparently due to virus like agents But the transmission of leukaemia in mammals cannot be accomplished at present except by the inoculation of cells into suitable susceptible animals In a recent review on the aetiology and nature of leukaemia Furth (1950) concluded that the essential change resided in the leukaemia cell and consisted of an acquired inability of immature leucocytes to respond to forces normally regulating their prolification and maturation Thus the leukaemia cell had acquired all the character of a neoplastic cell and in this connexion it may be stated that carcinogenic chemical agents (for example tar) and physical agents (for example x rays) which produce neoplastic conditions in the tissues such as the skin can also produce leukaemia

Acute leukaemia

Myeloblastic lymphoblastic

It is beyond the scope of this article to describe the clinical features and pathological types in detail For this the reader is referred to standard works on the subject but because of the great difference in response to treatment allusion must be made to type and age incidence

Although many reports avoid morphological classification as to cell types the observation of many others clearly show that it is in the lymphatic form of acute leukaemia in which the most consistent response to treatment is obtained Further it has been conclusively demonstrated that the age of the patient is of great importance The best results are without doubt obtained in children The remission rates in children under therapy are high—somewhere in the range of 50-60 per cent in the cases treated showing remissions of variable duration

whereas in adults the rate is 3–5 per cent (Sacks 1952) The acute lymphatic leukaemia of adults—unlike that in children—is unresponsive to treatment

Natural history of the disease—The disease is invariably fatal in a short period varying from weeks to a few months the average being less than 6 months Spontaneous remission does occasionally occur but reports indicate that it occurs in less than 10 per cent of cases (Birge Jenks and Davis 1949 Diamond and Luhby 1951) and is brief in duration

Treatment and progress—Until recent years the treatment of acute leukaemia was purely palliative Transfusion to correct anaemia and chemotherapy to control infection—particularly control of the distressing buccal ulceration The treatment with folic acid antagonists is included here because it is in conjunction with or in succession to the use of this group of drugs that ACTH and cortisone are most useful

In 1948 the first report of drug induced remissions was published (Farber and his colleagues 1948) The drug used was 4-amino pteroylglutamic acid (aminopterin) and was the first of a group known as the folic acid antagonists Several other drugs of this group have been synthesized but aminopterin and amethopterin remain the drugs of choice (Sacks 1952) Reports of many investigators in anaemia would indicate that in about 60 per cent of children a remission can be obtained by the use of these drugs The experience of the author with aminopterin is not nearly as favourable remission occurring in less than 20 per cent of a very small series of cases The doses recommended by Farber in children were 0 5–1 milligram of aminopterin daily or 3-5 milligrams of amethopterin daily depending on the age weight and physical condition of the patient Daily white cell counts and physical examination determined the total dosage Toxic effects are very serious and these drugs must be used with extreme care Ulceration of mouth and mucous membranes is one of the earliest signs of over-dosage and is rapidly followed by anorexia abdominal pain and diarrhoea The appearance of any of these signs except anorexia alone is an indication for

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frequent length of remission would appear to be 3–9 months after which cases appear to become resistant to the drugs and do not respond to their administration

At this point ACTH or better still cortisone may be used These hormone drugs have no relation whatever to the folic acid antagonists and yet from the reports so far available appear to be able to induce complete or partial remissions in at least 50 per cent of cases of acute leukaemia in children (Farber and his colleagues 1951) The pattern of the response is very similar to that produced by the folic acid antagonists That is to say that it is the acute leukaemia of children which responds and particularly the acute lymphatic variety Further these hormones may produce a remission in cases which have failed to respond to the anti folic acid group of drugs or which have become resistant to them There seems very little to choose between ACTH and cortisone on the basis of the results obtained so far—but cortisone has the inestimable advantage of being effective when given by mouth ACTH of course has to be given by injection The reason why these hormones may be effective is not understood nor is their mode of action From work on animals they would appear to have an inhibiting effect on lymphoid tissues causing a decreased production of lymphocytes (Dougherty and White 1944) but the reason for this is not understood

The dosage employed has varied considerably To some extent it depends on the age of the child The following scheme is suggested for ACTH under the age of 3 years 10 milligrams in four divided doses daily between 3–6 years 20 milligrams four times daily and above the age of 8 25–30 milligrams four times daily For cortisone 60 120 and 180 milligrams for the age groups quoted above again given in four divided doses daily The duration of therapy should be from 10 to 13 days depending on the response If no response is obtained at the end of 30 days the hormones should be discontinued and one of the anti folic acid group of drugs tried This should be done even if the patient has shown resistance to the drug before hormone therapy as there is

immediate cessation of therapy If toxic signs quickly disappear—as is usual if the drug has been cautiously administered—then therapy may be recommenced in a few days after the signs have disappeared When a remission either partial or complete has been obtained, a small maintenance dose (0 5–1 milligram of aminopterin) is given, 1–3 times a week according to the response and tolerance of the patient The maintenance dose of amethopterin varies between 1 milligram per day and 3 milligrams bi weekly In cases of prolonged therapy a diffuse partial alopecia is frequently seen but it is not regarded as an indication for stopping treatment Purpura and haemorrhage are two very common features of acute leukaemia and the author found haemorrhage an extremely troublesome complication which appears in a few cases at least to be made much worse and in one case seen personally uncontrollable during anti folic acid therapy In cases which are going to remit a result is often seen in the first 5 days or so and unless an improvement is evident by the end of the second and certainly by the end of the third week therapy should be discontinued as complete aplasia of the marrow has been described as a toxic effect The margin between the therapeutic dose and the toxic dose is exceedingly small and great care must be taken in administration of the drugs The clinical condition of the patient is at least as important as the leucocyte count and it cannot be too strongly emphasized that the patient must be seen every day The treatment of severe toxic effects is not easy nor very satisfactory Large doses of folic acid have been used and are ineffective both in man and animals (Heinle 1952) The use of citrovorum factor (folinic acid) has been reported as successful in both rats (Heinle 1952) and man (Schoenbach and his colleagues 1950) and so it would appear that the anti folic acid antagonists are really anti folinic acid antagonists

The remissions produced by these drugs vary in duration from a few days to more than 2 years although it must be pointed out that cases surviving as long as 2 years are in a very small minority and are quite exceptional The most

1951) the results are no better than those obtained with deep x ray therapy Further the cost of treatment is much greater in the case of the steroid hormones and the desired result is only obtained in a comparatively small number of cases treated Deep x ray irradiation can be relied upon to produce more constant and certainly more lasting results

Allied disorders

Lymphosarcoma and reticulum cell sarcoma

There are many reports in the literature on the use of these hormones in lymphosarcoma (Rosenthal and his colleagues 1951 Wintrobe and his colleagues 1951 Limarzi Paul and Best 1951 Farber and his colleagues 1951 Eliel 1951 Taylor 1951) From these reports it is clear that some improvement in the patient s clinical condition can be expected in about 50 per cent of cases and in a smaller proportion regression of the tumours also occurs The improvement in the clinical condition is manifested by increase in appetite and sense of well being and subsidence of pyrexia and pain if present But it is apparent that the results are not superior to those induced by deep x ray therapy and the nitrogen mustards and the use of these hormones for this disease is probably not justified

Hodgkin s disease

A number of published reports are available giving the results of treatment with ACTH or cortisone (Engle and Ban 1951 Rosenthal and his colleagues 1951 Limarzi Paul and Best 1951 Farber and his colleagues 1951 Eliel 1951 Taylor 1951) From these results it is evident that approximately 60–70 per cent of cases will show some clinical improvement but it is symptomatic only—the underlying disease remains Thus the size of the lymph nodes may be decreased and the haemoglobin and red cells may be increased (Strauss and his colleagues 1952) The occasional case in the terminal stages of the disease may be dramatically improved as was 1 case reported by Rosenthal and his colleagues (1951) The present position is that while the steroid hormones

some evidence that afterwards he may respond once more (Kingsley Pillers 1951, 1952) The response is classified under three headings (1) Complete remission (that is clinical and haematological), (2) partial (where clinical response is fair but leukaemia is still detectable in peripheral blood and bone marrow) and (3) no response The response of most patients will fall into the partial remission category From *the results available to date the remission rate is approximately* 50 per cent but the length of remission is somewhat shorter than with the folic acid antagonists—from 4 to 8 weeks being the usual duration There is some evidence that the use of folic acid antagonists combined with ACTH or cortisone may produce a somewhat higher remission rate (Stickney 1951)

Although one or more remissions may be produced as a result of therapy no case of cure has ever been recorded All cases eventually relapse and die

Monocytic leukaemia

It is generally agreed that in this type of leukaemia no known therapy has any effect on the disease process Most cases showed no response whatsoever to the steroid hormones (Report 1952a) or the folic acid antagonists (Report 1952b)

Chronic myeloid leukaemia

The steroid hormones have been tried and the results have been disappointing The only result reported is some diminution in the size of the spleen no other clinical or haematological benefit resulting whatsoever The administration of urethane or deep x ray irradiation to the spleen remains at the present moment the treatment of choice for this condition

Chronic lymphatic leukaemia

In this condition high hopes were held for treatment by the steroid hormones In fact these hopes have not been realized Although treatment with these hormones has occasionally resulted in a diminution in the size of the glands and a reduction in the peripheral leucocyte count (Eliel

response while actually on treatment In view of the fact that these patients may live for many years these hormones should be given a trial if the patient is anaemic They can do no harm and even if only the occasional case improves it is worth while

Carcinomatosis of the bone marrow —Carcinomatosis of the bone marrow is always secondary to carcinoma elsewhere—usually primary in bronchus breast kidney or prostate In children secondary neuroblastoma of the bone marrow may be seen occasionally Usually no good effect can be demonstrated but a few patients may feel better and their appetites may be improved But the fundamental condition is unaffected and therefore there is no point in giving these drugs

CONGENITAL HAEMOLYTIC ANAEMIA

Cooley s anaemia

Only a very limited number of reports are available to date on the results of treatment with the steroid hormones The severe form of the disease (thalassaemia major) is the only form requiring treatment Of the reports available to date 5 cases have been treated and a good response while on therapy was obtained in 3 cases in one the improvement was maintained for a period of nearly 3 months after treatment had ceased (Whitelaw 1951) More interesting was the fact that 1 child who showed improvement on a dose of 40 milligrams of ACTH daily was maintained on this dose as an outpatient in a satisfactory condition with a blood count of 4 2 millimetres per cubic millimetre over a period of 6 months (Schulman 1951) In addition to the haemopoietic improvement there was a marked improvement in her clinical condition and she showed a progressive gain in weight These children have to live a transfusion life—a complete remission is unknown The relief afforded by a 6 month interval from transfusions is very real but of course no cure can at present be produced and these cases constitute a very real problem in therapy This disease is quite common in the Mediterranean countries but cases are now being seen in Great Britain as a

may be valuable adjuncts to the treatment of this disorder by more conventional means for example nitrogen mustard they are not substitutes Their administration may result in *symptomatic clinical improvement* and decrease of anaemia and leucopenia which are so often present The doses used have varied greatly but are of the same order as those used in the treatment of the leukaemias

Multiple myeloma

Multiple myeloma may be regarded as an aleukaemic leukaemia affecting the plasma cell series Indeed plasma cell leukaemias have been reported ACTH and cortisone have been tried in a fair number of cases and the results published (Rosenthal and his colleagues 1951 Limarzi Paul and Best 1951 Farber and his colleagues 1951 Eliel 1951 Taylor 1951 Rosenburg and his colleagues 1951 Wintrobe and his colleagues 1951 Engle and Ban, 1951) From the published results available it is clear that most cases do not respond The occasional case manifests a marked improvement but it would seem that the usefulness of these hormones is very strictly limited and that their general use for this condition is not justified

Miscellaneous bone marrow conditions

Myelofibrosis —In this condition the pathology is a replacement of the bone marrow cells by inactive fibrous tissue In many cases this replacement has gone so far that there is so little space left for active bone marrow that the extra medullary sites of blood formation (such as the spleen and the liver) have to be pressed into production to produce sufficient cells and maintain life Many cases require periodical blood transfusions Since there is evidence that ACTH and cortisone stimulate the haemopoietic tissues (Hudson Herdan and Yoffrey 1952) it would be rational to administer ACTH and cortisone to these patients for this purpose Several cases have been treated (Report 1952a Wintrobe and his colleagues 1951) but the results are far from encouraging—only 1 of the 6 cases recorded being improved and this only a partial

ACQUIRED HAEMOLYTIC ANAEMIA

Erythroblastosis foetalis

The development of antibodies by the pregnant mother which destroy the erythrocytes of the foetus and produce anaemia jaundice and hydrops is the cause of this condition Some infants are mildly affected and live with or without treatment but many others are stillborn or die soon after birth Many remedies have been tried but none has been effective in preventing this disease which develops *in utero* and often results in stillbirth In most cases it would appear that the period of maximal damage to the foetus is from the twenty eighth week of gestation onwards Naturally this led to the assumption that the induction of labour some 4–6 weeks before time would give beneficial results Unfortunately in practice this prematurity does not result in the hoped for increase in survival rate owing to the increased incidence of kernicterus As cortisone and ACTH have given good results in acquired haemolytic anaemia it would seem logical to attempt to control the disease in the foetus by the administration of these drugs to the mother during the last 4–12 weeks of pregnancy Very little work has up to the present time been reported on the use of the steroid hormones in this condition but an encouraging report in one case has recently been published (Meyers and his colleagues 1952) In this case a woman in her third pregnancy was treated for a period of 4 weeks (thirty third to thirty seventh week) with cortisone 100 milligrams per day At the end of the thirty seventh week labour was induced and she gave birth to a live infant which manifested a mild form of the disease Recovery followed upon an exchange transfusion This patient had had a normal infant from her first pregnancy—the second had resulted in a severely affected baby at 37 weeks which died after 32 hours Throughout her third pregnancy she had a high titre of incomplete anti D (1/64–1/512) in her serum and the birth of a mildly affected infant without treatment was not to be expected Since no other treatment is available at present steroid therapy deserves every trial It must be emphasized that therapy must

result of the settlıng of evacuees from Malta Cyprus and Greece durıng World War II and the numbers are lıkely to ıncrease

Acholurıc jaundıce

A number of cases have been treated wıth ACTH and cortısone (Report 1952a , Davıdson and hıs colleagues 1951 Lımarzı Paul and Best 1951) but no response has been noted ın any case In vıew of thıs remarkable unanımıty of opınıon ıt can be confidently stated that no good results can be expected from the use of these hormones ın thıs condıtıon

Sıckle-cell anaemıa

There are only three reports avaılable ın the lıterature on thıs condıtıon (Sass 1952 Kass and hıs colleagues 1951) Sass treated one case—a 20 year old negress—and obtaıned a dramatıc clınıcal ımprovement wıth complete regressıon of symptoms on 100 mıllıgrams of ACTH or cortısone daıly Reductıon of the dose or cessatıon of therapy resulted ın relapse At the tıme of the report approxımately 3 months after commencement of treatment the patıent ıs descrıbed as well and gaınfully employed and completely asympto matıc on a maıntenance dose of 100 mıllıgrams of cortısone daıly Thıs ıs a truly remarkable result ın the treatment of an otherwıse almost untreatable dısorder Kass and hıs colleagues (1951) treated 2 cases—one an 11 year old negress and the other a 21 year old negro They were treated wıth 100 mıllı grams of ACTH daıly In both the hormone appeared to make the patıent worse at first but later ımproved the older patıent He had been observed sınce ınfancy and hıs erythro cyte count whıch had fluctuated between 2 4–2 8 mıllımetres rose to 4 2 mıllımetres and retıculocytes fell from 12–20 per cent to 2 5 per cent Thıs was assocıated wıth other sıgns of decreased haemolysıs as fallıng serum bılırubın and faecal urobılınogen In the negress ACTH was dıscontınued and 5 mıllıgrams daıly of cortısone gıven wıth no change A second course of ACTH precıpıtated a further crısıs

No firm conclusıons can be drawn from so few cases but further trıal ıs ındıcated

withheld unless absolutely essential to save life that is haemo globin levels below 5 grammes per 100 millilitres The cross matching of the blood for transfusion is a most difficult problem and in fact it will probably be found that no blood is wholly compatible, this is again not surprising since the patient s serum agglutinates his own erythrocytes if they are suspended in albumen

The administration of the steroid hormones results in many cases in a modification of the course of the disease In most cases the haemolytic process can be controlled and many arrested especially if full doses are used In fact Rosenthal and his colleagues (1952) have stated that as a result of their experience of the use of steroid hormones that medical manage ment is to be preferred They found that most of their 17 patients treated responded and felt better almost immediately There was a reticulocytosis a rising red cell count and longer red cell survival a fall in the serum bilirubin and faecal urobi linogen and that with these changes the need for blood trans fusions ceased abruptly In 4 of their cases the direct Coombs s reaction became negative The dosage used varied widely from case to case—from 100–300 milligrams daily of cortisone commencing at the lower dose and increasing it rapidly if necessary until control of the haemolytic process was obtained The treatment was continued for from days to months as indicated by the progress of the case Of course such toxic manifestation as marked fluid retention and hypokalaemia are likely to develop with large doses and would of themselves necessitate a reduction or even temporary cessation of the administration of the hormones

The experience of investigators in the United States of America would appear to confirm these favourable results (Wintrobe and his colleagues 1951 Limarzi Paul and Best 1951) Meyers and his colleagues (1952) treated 7 cases of idiopathic haemolytic anaemia with full doses of ACTH or cortisone All 7 patients were improved but only in 1 case was an incomplete remission obtained Of the remaining 6 cases all were described as having complete remissions

commence early enough in the pregnancy to be effective and that all facilities for exchange transfusion should be available To give the child the best chance it is probably wise to exchange transfuse as soon as possible after birth in all but the most mild cases of erythroblastosis Cortisone has also been administered to the child (Whitelaw 1951) after birth in order to control the haemolytic process but not enough data is available to say definitely that this achieves the desired effect

Idiopathic and symptomatic acquired anaemia

Acquired haemolytic anaemia presents two forms—idio pathic and symptomatic

In symptomatic acquired anaemia there is evidence of some other condition most commonly chronic lymphatic leukaemia lymphosarcoma or Hodgkin s disease (some cases associated with drugs are not considered here)

There does not appear to be any fundamental difference between the two types as far as the haemolytic anaemia process is concerned In both types the fundamental pathological change is the elaboration of antibodies by the patients own tissues against their own erythrocytes This can be demon strated by a Coombs s test or other tests for circulating haemolysins (Dacie and de Gruchy 1951)

Treatment

Until the advent of the steroid hormones the only treatment available was splenectomy and repeated blood transfusions Repeated blood transfusions in this type of anaemia—in contrast to the congenital type—do not afford much relief This is to be expected since there is evidence of a circulating antibody in the serum and in the fact that there has been proof that the transfused cells have a much reduced survival time (Dacie and Mollison 1946) In fact in a really acute haemolytic crisis the transfused cells may only survive a matter of a few days and in these circumstances are more likely to embarrass an acutely ill patient who already has more than enough of the breakdown products of haemolysed erythrocytes In acquired haemolytic anaemia transfusion is probably best

remission was obtained which lasted with minor exacerbations for about 1 year Then the patient developed an acute haemolytic episode and *failed to respond to 200 milligrams of cortisone* In the second case a partial remission was obtained with 100 milligrams of cortisone daily (4 divided doses by mouth) and further improvement has been obtained with a splenectomy

The reason for the action of the steroid hormones is not understood It has been suggested that they act by depressing antibody formation (Kass and his colleagues 1951) or by interfering with the antigen union or some product of this union (Mirick 1951) Work in experimental animals would seem to indicate that neither of these hypotheses is correct (de Vries 1900, Clearkin 1952) In human subjects the *response of the antibody titre is very variable In some cases* it is found to be depressed in others no change is detected although clinical remission is obtained So at the present time the use of the steroid hormones is empirical Most cases respond at least in part for reasons which are not understood Also it must be accepted that a minority of cases apparently similar in every respect do not respond and the reason for this difference cannot be given

Paroxysmal haemoglobinurias

Haemoglobinuria is caused by intravascular haemolysis and may occur as a symptom of almost any haemolytic anaemia *But there are certain clinical conditions which are* characterized by paroxysms of haemoglobinuria

Cold haemoglobinuria

This is caused by exposure to cold and is associated with syphilis either congenital or acquired Treatment consists of treating the causal syphilis (Whitby and Britton 1950) This condition need not be further considered here

Haemoglobinuria from exertion

This is rare and relatively harmless

Nocturnal haemoglobinuria

This disease *is always associated with a haemolytic anaemia* The haemolytic episodes occur during sleep whether this is

In 4, relapse occurred promptly when therapy was discontinued In 2, the remission was continued for some months in 1 case 6 months and in the other for more than 15 months The doses of ACTH employed were 100–160 milligrams daily for 11–36 days or 300 milligrams of cortisone daily for 19–28 days One of their cases however, received nearly 30 grammes of cortisone and nearly 1 gramme of ACTH and a splenectomy before complete remission was attained The 5 cases which relapsed all had a splenectomy and further courses of ACTH or cortisone They found that intensive courses of ACTH or cortisone in the immediate pre operative period did not interfere with normal wound healing and that failure to respond to these hormones did not preclude therapeutic response to splenectomy Further, patients with incomplete remissions after splenectomy may be benefited by steroid hormone therapy

Some British results are available The preliminary report to the Medical Research Council by the panel on haematological application of ACTH and cortisone (Report 1952a) *stated that 3 out of 11 cases had a good response which was* continued for at least 1 month after stopping treatment A further 6 cases showed a partial response and in 3 of these the good effects continued for at least 1 month after administration of the hormones had ceased No response was obtained in 3 cases

Earlier in the year Clearkin (1952) reported the results of treatment in 2 cases which received 100 milligrams of ACTH daily in 4 divided doses for 6–16 days One case treated for 6 days improved dramatically and maintained a normal blood picture when therapy was discontinued This case had a positive Wassermann reaction In the second case a rise of 10 per cent in the haemoglobin and a jump in the reticulocytes from 26 to 51 per cent were the only signs of improvement The haemolytic process apparently was intensified and there was evidence of an increased erythrocytic destruction This case had a negative Wassermann

The author has experience of 2 cases In the first case (which also had a lymphatic leukaemia) a slowly developing

Best, 1951 Rosenburg and his colleagues 1951) In sharp contrast to this Hill and Hunter (1951) report on 4 cases In 1 case a prompt reticulocyte response was observed and was followed by a rise in the red cell count and elimination of the need for transfusion In the remaining 3 cases little response was apparently obtained at the time of therapy but after transfusion and discharge from hospital on routine treatment (liver injections vitamin B_1 cobalt) the patient s haemoglobin was found to stabilize at approximately normal levels without further transfusions These results may be said to be truly remarkable as these patients are normally refractory to all forms of treatment Loeb (1951) reports on 6 cases of which 5 showed improvement He found the splenectomy increased the haemoglobin still further but warns that a good therapeutic result can only be obtained in a minority He also suggests that those cases which show increased erythro cytic activity after administration of the steroid hormones are the ones which do best after splenectomy

Since these hormones with or without splenectomy offer the only real hope of treatment they should always be tried In the event of their failure the patient is condemned to a transfusion life The hormones should always be used in full doses for example 100–160 milligrams of ACTH or 200–300 milligrams of cortisone daily After a reasonable trial (2–4 weeks) without improvement they may be discontinued but the possibility of a delayed response as described by Hill and Hunter (1951) should be borne in mind

Secondary aplastic anaemia—Secondary aplastic anaemia caused by drugs or chemical poisons is an extremely serious and nowadays uncommon condition If the response of the leucocytes to the steroid hormones in agranulocytosis caused by similar agents is any indication then a favourable result may be expected However there are no reports available in the literature and it must always be remembered that aplasia of the bone marrow represents a very severe toxic change and other organs are almost certainly bound to be seriously affected and this will militate against recovery

taken by day or by night There are usually long periods of freedom from haemoglobinuria though other signs of haemolytic anaemia are present It has been suggested that lysis occurs in sleep because then there is a decrease in the *p*H in the blood and it has been found that the red cells of these patients are susceptible to a potential haemolysin active at *p*H 7 0–7 2 Treatment is very difficult and transfusion of erythrocytes washed free of all plasma, as recommended by Dacie (1949), is probably the best

ACTH and cortisone have not been used in many cases but the response in the ones treated so far has not been encouraging (Report 1952a Kalant and Donat 1952) There is no reason to think that any further experience will alter the outlook for these hormones in this particular disorder Because of this complete lack of response it is important to differentiate this condition from other acquired haemolytic anaemias The haemoglobinuria may be relatively trivial and the continued signs of chronic haemolytic anaemia in the absence of haemoglobinuria may cause difficulty Under these circumstances the Coombs s test (usually negative in this condition but positive in idiopathic acquired haemolytic anaemia) and Hams s test (acid fragility) which is positive in haemoglobinuria may give valuable aid

Dyshaemopoietic anaemias

Aplastic anaemias (refractory anaemias)

These anaemias may be either normocytic or macrocytic The bone marrow may be either hypoplastic or hyperplastic The leucocytes and platelets are both markedly reduced Two forms of the disease are recognized primary or idiopathic and secondary due to x rays poisons and drugs

Primary aplastic anaemia —A number of cases have been treated by several groups of workers with varying results Wintrobe and his colleagues (1951) treated 3 cases Two showed subjective improvement with some increase in neutrophils and capillary fragility Many other workers share this depressing experience (Report 1951a Limarzi Paul and

Anaemia of disseminated lupus erythematosus —All patients suffering from disseminated lupus have anaemia of some degree—usually slight to moderate ACTH and cortisone are often administered to these patients and the resulting benefit may include some improvement in the anaemia (Ellington and his colleagues 1949) but this is by no means a constant finding (Soffer and his colleagues 1951) Associated with the anaemia is also a leucopenia which may also improve on steroid hormone therapy (Soffer and his colleagues 1951) However both the anaemia and the leucopenia are only a small portion of the general disease and are far less serious than many of the other manifestations

As a general statement it may be said that anything which improves the disease will also improve the anaemia

Anaemia of nephritis —It has been reported by Farnsworth (1950) that the anaemia in acute and subacute glomerulo nephritis was improved when treated by ACTH However anaemia is not a troublesome feature of these diseases and the use of ACTH or cortisone for this purpose alone is not indicated

The anaemia of chronic nephritis is much more severe and is completely refractory to the ordinary treatment by haema tinics In general it may be said that it improves only when the uraemia improves However treatment with steroid hormones has improved the anaemia in some cases (Klin 1951)

Anaemia of chronic liver disease (*cirrhosis of the liver*) — Some encouraging reports have been published concerning the beneficial effect of short courses of ACTH to patients with cirrhosis of the liver (Bongiovanni and Eisenmenger 1951) Owing to the fact that many of these patients are suffering from chronic ascites and these hormones are often accompanied by fluid retention special care has to be taken in their administration and a special watch kept for signs of gross fluid retention Brown (1951) reported his results in giving 70–200 milligrams ACTH daily for 10–15 days to 4 patients with cirrhosis and in addition to marked improvement in their clinical condition the anaemia also present improved

Thiersch and his colleagues (1952) report unfavourably on the results of the use of these drugs on marrow regeneration following irradiation

Pernicious anaemia

The effect of these hormones on pernicious anaemia has been investigated by several workers (Wintrobe and his colleagues 1951 , Rosenburgh and his colleagues 1951 Lowenstein and his colleagues 1951) No beneficial result in any way comparable with liver or vitamin B_1 therapy has been obtained

The anaemia of rheumatoid arthritis—Almost all cases of rheumatoid arthritis have some degree of anaemia though usually only of moderate severity The anaemia is usually microcytic and slightly hypochromic but may be normochromic It is most resistant to treatment no response being obtained with iron or liver therapy or any of the usual haematinics Indeed until the advent of the steroid hormones there was no drug which had any effect In addition to their general effect on the arthritic condition of the patient administration of these hormones is accompanied by a reticulocytosis and there after an increase in the red cell count and haemoglobin The peak reticulocyte count is usually reached some time in the second or occasionally in the third week of therapy (Copeman and his colleagues 1952 Finch and his colleagues 1951a) There after the haemoglobin and erythrocyte counts rise to normal levels in most cases There are changes in the leucocytes a polymorphonuclear leucocytosis being observed in many cases (Finch and his colleagues 1951b)

Anaemia of rheumatic fever—No reference will be made in this article on the value of ACTH or cortisone in the treatment of rheumatic fever Encouraging results have been reported and in addition to the other beneficial results there has been an improvement in the anaemia associated with the disease (Hench and his colleagues 1950) Since the anaemia is usually only of slight degree this effect is not of great value It is just part of the generalized improvement in body function brought about by the administration of these hormones

(50–75 milligrams daily) for a period of 16 weeks Then the drug had to be stopped on account of such undesirable side effects as hirsutism skin striae and rounding of the face These workers conclude that ACTH or cortisone induces improvement in the vascular resistance which is not necessarily accompanied with increased platelet production although in their 2 cases with complete remissions a normal platelet count was achieved Further these hormones do not interfere with the occurrence of a spontaneous remission nor with a remission induced by splenectomy

There can be no doubt that the improvement in capillary resistance which can be obtained with the administration of ACTH (dose of 100–120 milligrams daily) or of cortisone (100–200 milligrams daily) will control the haemorrhagic phenomena of most cases They can therefore be of the greatest assistance in the management of a case in the acute phase and can either be continued until a spontaneous remission occurs or just to control the case prior to splenectomy Further cases which relapse after splenectomy may benefit considerably during ACTH or cortisone therapy

Symptomatic purpura

Allergic purpura (*Henoch Schonlein purpura*) —There are a few reports in the literature on the results of ACTH or cortisone therapy in this condition Some cases appear to respond promptly (Woolley 1952 Kugelmass 1951) while others do not respond at all (Limarzi Paul and Best 1951) In view of the improved vascular resistance found by Falcon Greene and Loyner (1952) one would expect some response in the majority of cases

Toxic purpura —These are purpuras arising directly as a result of some bacterial chemical or physical toxin There may or may not be an associated thrombocytopenia They may be secondary to other generalized diseases such as leukaemia aplastic anaemia and disseminated lupus erythematosus The treatment of such a heterogeneous group of disorders is bound to give varying results There seems little doubt that the purpuras occurring with aplastic anaemia

in all 4 cases This was not a temporary phenomenon in his cases and was not due to haemoconcentration because he measured the plasma volume in all cases

The purpuras

Idiopathic thrombocytopenic purpura

The treatment of a patient suffering from an acute haemorrhagic episode has always presented a serious problem Hitherto blood transfusion with fresh blood has been the only method available But now there are many reports in the literature on the value of ACTH and cortisone in this condition (Report 1952a Meyers and his colleagues 1952 Wintrobe and his colleagues 1951 , Limarzi Paul and Best 1951 Falcon Greene and Loyner 1952) Thus Meyers and his colleagues (1952) treated 17 cases with ACTH (100 milligrams daily) and obtained complete sustained remissions lasting from 16 to 12 months after cessation of therapy in 5 cases During therapy there was evidence of improvement in the capillary fragility as well as a rise in the platelet count and in the 5 cases referred to above these changes persisted for many months after therapy was discontinued They also found that complete remissions were obtained in 7 further cases but these relapsed promptly when hormone treatment was discontinued The remaining 5 patients responded poorly These workers emphasize that ACTH or cortisone therapy does not interfere with wound healing when given in the immediate pre operative period prior to splenectomy and that failure to respond to them does not preclude a therapeutic response to splenectomy They find also that patients who have already undergone splenectomy and have only incomplete remissions may be benefited by courses of ACTH or cortisone Falcon Greene and Loyner (1952) studied the effect of ACTH or cortisone on 4 cases and in 2 obtained a complete remission Their cases received 40–150 milligrams of ACTH daily or 50–200 milligrams of cortisone and some of the patients received more than one course of treatment Indeed 1 patient who responded but relapsed quickly after therapy was stopped was kept in remission by a maintenance dose of cortisone

The treatment of this condition presents great difficulties and whilst the antibiotics have reduced considerably the hazard from infection there still remains the problem of raising the leucocyte count and especially the granulocyte count to normal levels Treatment by all the known and time honoured remedies should be tried that is liver extract *folic acid and pyridoxine but the place of the nucleic acid* derivatives such as pentose nucleotide is now doubtful However in many cases all these remedies have very little effect and in the cases which fail to respond ACTH or cortisone can be tried Both these hormones are powerful stimulants to the leucopoietic tissue in the normal man and their use would appear to be rational In some cases good results have been reported (Bethell Miller and Meyers 1951) but the results appear to be variable as others have had no success (Wintrobe and his colleagues 1951) In any case their administration *if properly controlled* can do *no* harm and is well worth a trial The dosage scheme suggested is as follows ACTH 100 milligrams daily in 4 divided doses daily for 10 days or cortisone 100 milligrams daily also in 4 divided doses If after 5 days the desired result is not attained and patient is not markedly improved it is suggested that the doses of ACTH be increased by 40-60 milligrams daily or the dose of cortisone doubled Cortisone may be raised to 300 milligrams daily if required If after 10 days no beneficial result is obtained the drug may be discontinued care being taken to taper off the dosage over 3 or 4 days halving the dose each day If a good result is obtained the same procedure may be adopted to see if the improvement is maintained If it is not the hormone should be given again and it may prove possible to maintain the count on a maintenance dose Meanwhile opinion should be sought as to whether the case might not be one of splenic neutropenia which might be expected to benefit from removal of the spleen In this event the improvement is likely to be maintained only while the patient is on the drug but splenectomy should result in more permanent benefit

(Ragan 1951) acute leukaemia (Falcon Greene and Lovner 1952) and disseminated lupus erythematosus can all be much improved by ACTH or cortisone therapy The administration of these hormones in purpuras caused by chemical agents has occasionally met with success (Report 1952a) but in many cases mere withdrawal of the injurious drug or compound is sufficient

In the purpuras due to infection considerable care must be exercised in choosing cases because of the well known effect of ACTH and cortisone in suppressing clinical signs of infection and inflammation Indeed there is considerable evidence that some infections such as tuberculosis, may be activated (King and his colleagues 1951) However when combined with chemotherapy they may prove life saving in such conditions as the Waterhouse Friderichsen syndrome (Nelson and Goldstein 1951) in which haemorrhagic phenomena are a conspicuous feature

Typhoid fever may also develop a toxic purpura Only one report dealing with the administration of ACTH to 2 cases of typhoid fever is available (Roche, 1951) and although the general condition of the patient was greatly benefited and no untoward results reported no mention is made of purpura or other haemorrhagic phenomena in these cases

Agranulocytosis and granulocytopenia

Primary idiopathic

Agranulocytosis and granulocytopenia have been grouped together because the difference between them is one of degree only Granulocytopenia implies a decrease in the granulocytes (polymorphonuclears) below the normal limit of 3 000 per cubic millimetre—usually to 2 000 or less per cubic millimetre By agranulocytosis is meant an extreme reduction in the granulocytes—always less than 1 000 per cubic millimetre and sometimes these cells are absent from the periphal blood altogether In any case the reduction is so extreme that symptoms due to lack of these essential cells such as ulceration of mucous membrane are present

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Secondary agranulocytosis or granulocytopenia

The causes of this condition are very numerous and the reader should consult standard works of medicine or haematology for a full classification Except in the case of granulocytopenia due to such physical agents as x rays (Thiersch and his colleagues 1952) it would appear that administration of ACTH or cortisone in the doses mentioned above in the treatment of the primary condition may accelerate the return of the polymorphonuclear leucocytes to normal levels (McMillan 1951, Hart Wraith and Mansell, 1952) In the 2 cases referred to above ACTH therapy was commenced when the patient had failed to respond to the usual therapy, including withdrawal of the offending drugs and their clinical condition had deteriorated considerably In both instances, rapid improvement followed and was accompanied by a return of the leucocyte count to well above normal levels These effects were of course, maintained after the hormones were discontinued These results are most encouraging and it is apparent that ACTH or cortisone can stimulate leucopoiesis and return of the granulocytes to the periphal circulation in cases of this kind The use of these drugs is definitely indicated in any patient suffering from any agranulocytosis (except perhaps that due to x rays) especially if mere withdrawal of the offending agent is not followed by a prompt recovery

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